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"Acta Orthopaedica Et Traumatologica" is the official journal of the Hellenic Association of Orthopaedic Surgery and Traumatology, first published in 1948. This revived edition of Acta Orthopaedica Et Traumatologica, published in English, aspires to promote scientific knowledge in Orthopaedics and Traumatology worldwide. It is a peer-reviewed Journal, aiming at raising the profile of current evidence-based Orthopaedic practice and at improving the scientific multidisciplinary dialogue. Acta Orthopaedic Et Traumatologica Hellenica presents clinically pertinent, original research and timely review articles. It is open to International authors and readers and offers a compact forum of communication to Orthopaedic Surgeons and related science specialists.

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Patient anonymity should be ensured. All identifying data (name, identification numbers, initials) must be removed from text, images and tables. If it is mandatory for a patient's face to be included in the manuscript, the eyes should be sufficiently masked. If there is a possibility that a patient may be identified from a photograph or relevant legend and text, the patient's written consent should be submitted.

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or

Papaioannou NA, Triantafyllopoulos IK, Khaldi L, et al. Effect of calcitonin in early and late stages of experimentally induced osteoarthritis. A histomorphometric study. *Osteoarthritis Cartilage* 2007; 15(4): 386-95.

- Book chapters:

Triantafyllopoulos IK, Papaioannou NA. The Effect of Pharmacological Agents on the Bone-Implant Interface. In: Karachalios Th. (ed). Bone-Implant Interface in Orthopaedic Surgery. Springer – Verlag, London 2014, pp 221-237.

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ACTA ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

ACTA
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CONTENTS

The paralytic arm of Kaiser Wilhelm B

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ABSTRACT

Through exploring unknown aspects of history, we often discover details that are carefully hidden or written in the margins in fine print. In the context of research, the disability of Kaiser Wilhelm B could not go unnoticed. His paralyzed and atrophic left arm clearly defined his childhood, shaped his character and significantly affected his self-confidence, while providing an opportunity for parents and educators to channel their own obsessions. The decisions that Kaiser made in critical situations when he came of age, especially those that directed the destinies of the peoples of the world, were clearly affected by his physical deficit. Until recently, the medical view of Kaiser's disability pointed to traumatic paralysis of the brachial plexus during his birth. The diagnosis of obstetric palsy of the upper type (Erb's type) provided a complete explanation for the image we have of his left upper extremity, as depicted in paintings and portraits or assessed in the few videos and photographs of the time. However, a new point of view comes to shed light on the matter and orient the diagnosis in another direction.

KEYWORDS: obstetric; paralysis; brachial plexus; Kaiser Wilhelm B; First World War

Introduction

Among the main causes that led to the outbreak of the First World War were the geopolitical circumstances of the time and the widespread nationalism that encouraged rampant and dangerous armaments. And at the same time, the course of events was influenced by the imperialism of the powerful which encouraged risky decisions, political rivalries and economic pursuits. The assassination of the heir to the throne of Serbia, Archduke Franz Ferdinand, in Sarajevo of Bosnia on 28 June 1914, served only as a trigger to generate procedures. The reasons for the domino of events that would follow were deeper.

The millions of victims in the trenches of the rival factions, added to those of the Spanish flu, were merely the epilogue of a merciless universal confrontation. A confrontation that lasted four and a half bloody years and culminated in the collapse of powerful empires, the change of the world map and the humiliating defeat of Germany, events that paved the way for the outbreak of another Great War!

Childhood and influences

Wilhelm B of Germany (his full name in German

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Friedrich Wilhelm Viktor Albrecht) was born on January 27, 1859 in Potsdam, near Berlin. Fate had planned for him to rule as emperor of the German state and, at the same time, as King of Prussia from 1888 until the end of the First World War. Origin, geopolitical circumstances and the warlike aspirations of his countrymen prescribed his course as a sequence of inescapable developments.

Wilhelm was the eldest child of Prince Frederick (later emperor Frederick III) and Victoria, eldest daughter of Queen Victoria of Great Britain. The father failed to instill in his tender soul virtues such as courage and determination. He was honest and intelligent, he had respect for others, but he was not distinguished by will and fortitude. In contrast, the mother was characterized by completely different qualities. She had inherited from her father, the royal husband Albert, determination and stubbornness in her pursuits and from her mother strong emotions and self-confidence. She often subordinated her intelligence to the dictates of her emotions.

Victoria had an additional problem to deal with, after the birth of Wilhelm. The little boy had a disability in his left arm, which remained forever atrophic. Photographs from the time and the few film records show Wilhelm at various stages of his political and military career holding his crippled left arm with his right or artificially hiding it in his coat **(Figure 1)**. The mother tried to impose on her son the mentality of the "liberal 19th century British" and to raise him as an English nobleman. It escaped her that Wilhelm harbored negative feelings for the British, because in the person of the British obstetrician who had brought him to life, he saw the only person responsible for his disability. Victoria made him turn more towards those who represented the *Prussian ideal*, seeking that her son should adopt the virtues of a ruler, become brave, fair and resolute, and imbued with feelings of self-sacrifice, self-reliance and independence [1].

The relations between mother and son, under these circumstances, were constantly stumbling upon obstacles. Her influence on him was deep and continuous. He himself never managed to shake it off, nor to shed the vaunted respect for liberal values and way of life. His temperament did not conform to the tough warrior-king type, and he quickly realized that this was the only role he had to live up to with every sacrifice. He was constantly weak in controlling his actions, often drifting into excesses.

A constant struggle was going on in young Wilhelm's soul. On the one hand his inner inclinations, and on the other the sense of duty instilled in him by his Calvinist tutor, exerted countervailing forces as they alternated within him constantly, neutralizing each other. The tension between them, combined with his physical disability, generally explains his nervous, irritable and indecisive character [2].

In 1881, Wilhelm married Princess Augusta Victoria of Schleswig-Holstein, a woman who was unimaginative, without spiritual interests, untalented, a listless creature who made him bored and encouraged his reactionary tendencies. But she was the partner who represented stability in his life. And she was the wife who gave birth to six sons and one daughter. Their daughter Victoria Louise (1892-1980) married Ernest Augustus, Duke of Brunswick. Through their marriage, their daughter Frederica was born, later Queen of Greece and mother of the heir to the Greek throne Constantine, in the years preceding the dictatorship of the colonels [3].

Brachial plexus paralysis

The brachial plexus in the human body is a network of spinal nerve fibers, formed by the anterior branches of the four lower cervical roots (C5-C8) and the upper thoracic root (T1). It develops through the neck and axilla, ending in the upper extremity with peripheral nerves (mainly the axillary, musculocutaneous, radial, median and ulnar) which are responsible for the functionality, sensation and movement of the various joints. In other words, the brachial plexus is responsible for the proper functioning of the upper limb, with two exceptions: the trapezius muscle, which is innervated by the accessory nerve, and an area of skin adjacent to the axilla that is innervated by the intercostobrachial nerve.

During delivery, brachial plexus may be injured **(Figure 2)**. We don't know what was going on in the mid-19th century, but today's statistics put the

Figure 1. *Wilhelm as a child, October 1863.*

incidence of obstetric paralysis at rates ranging from 0.63 to 2.6 (and sometimes up to 5) cases per 1,000 live births. The incidence remains constant nowadays, despite the improvement of obstetric techniques.

Predisposing factors are considered: macrosomia, multiple pregnancies, a previous similar development, heredity, diabetes mellitus, overweight of the newborn, as well as the projection with which the fetus descends into the uterus shortly before delivery.

We do not know exactly the way the British obstetrician chose to bring about the birth of young Wilhelm. However, we are convinced that the mechanism of injury to the brachial plexus can occur either by violent abduction and external rotation of the upper limb, or by a strong downward push of the shoulder, or by a combination of these during childbirth **(Figure 3)**. When the damage concerns the upper roots (C5 and C6) it is called *Erb type palsy* and is sometimes combined with an injury of the C7 root.

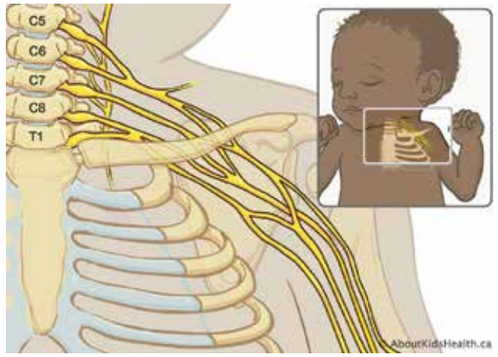

Figure 2. *Schematically, the brachial plexus and its branches in the upper limb.*

More rarely, when the damage affects all the roots (C5-T1) there is *total palsy*, while when it affects only the lower roots (C8 and T1) it is called *Klumpke type palsy*.

The brachial plexus palsy in Wilhelm's case was of the upper type (Erb) and this explains his inability to raise the shoulder or bend the elbow or turn the palm upwards. However, he was able to hold objects with the fingers of his left hand, such as his sword in official ceremonies. We must point out that -as then, so now- the mother is not responsible for the palsy. Likewise, the obstetrician and nursing staff are also not liable. And sometimes the severity of the damage is small (neuroapraxia), self-healing in 3-4 weeks, while sometimes it is severe (detachment of the roots in the spinal cord), where no automatic recovery is expected [4].

Kaiser Wilhelm B was unlucky because he was born at a time when electrophysiological testing, computed tomographic and magnetic myelography, i.e. the modern diagnostic methods that clearly approach the damage, had not yet been put to the service of Medical Science. Nor could, with the data of that time, his parents trust any of the surgical techniques that are currently applied with optimistic results. Tendon transfers have been replaced by brachial plexus repair, identification of the lesion, and repair with nerve grafts. Microsurgery techniques, in the hands of specialized surgeons, can now yield amazing results. Kaiser was not treated. Growth of

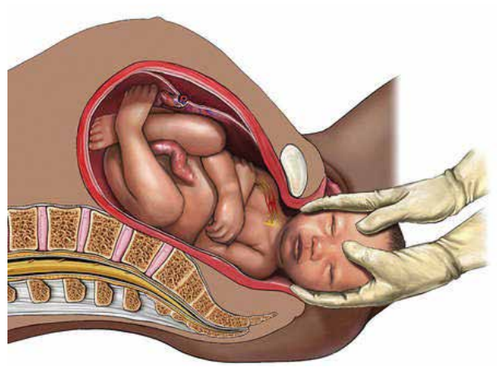

Figure 3. *During normal childbirth, the brachial plexus is injured.*

Figure 4. *Kaiser and his generals, at the start of the Great War.*

the left upper limb was delayed, remained short and progressively showed deformities and stiffness, both at the shoulder and at the elbow [5].

A relatively recent publication sheds new light on this issue, orienting the diagnosis in another direction. The study comes from Canada's *Lois Hole Hospital for Women* and is signed by Indian-origin Professor of Gynecology and Obstetrics Venu Jain and his colleagues. The authors evaluate a drop of Wilhelm's mother in the fourth month of pregnancy and note the deficit weight of the newborn. They claim that, on the occasion of the fall of the Empress Victoria, there was an arrest of the development of the fetus, due to detachment of the placenta. Then, relying on ultrasound measurements, they experimentally demonstrated that placental abruption usually impedes the blood flow directed to the left upper limb, and not to the right. They went even further, when they called the emperor's disability "Kaiser Wilhelm syndrome", replacing the older term, Erb's obstetric paralysis [6].

The role of Wilhelm in affairs

After Ferdinand's assassination, Austria-Hungary ordered general mobilization, declaring war on Serbia and bombarding Belgrade on 28 July. Russia attacked on July 30, in response to Serbia's request to stand by as an ally and helper. The Kaiser's Germany was waiting for this occasion and not only proposed to Austria-Hungary its participation in military operations for alleged revenge against Serbia, but had also promised full support. Then, with Russia's involvement, Germany responded by mobilizing against it without qualms. By intending to invade France, violated the neutrality of Belgium.

General mobilization caused the contending forces to be in a frenzy of excitement, ready to teach each other a lesson, hoping for a happy outcome and an end to the war before Christmas of that year. The illusions of a bohemian life promised by the carelessness of the *Belle Époque*, together with the leaps in science and technology that gave the assurance of a lasting peaceful future, removed the possibility of imminent struggle. And yet, a veritable domino of development eventually led to global conflict.

After all, things showed from before, the prevailing generalized instability. After Wilhelm assumed power, certain movements marked his pursuits, setting the stage for the upcoming events. When he took over the administration of his country, he was only 29 years old, and everyone in Germany believed that he would amend the Constitution and make the chancellor responsible to the Reichstag. The events belied the hopes. In March 1890, Wilhelm forced Bismarck to resign as chancellor. It is true that Bismarck was no longer the right man to solve the problems he had caused by the creation of the German Empire. The Kaiser's action would be justified if he had a concrete solution ready. His unstable temperament, however, soon led him to

Figure 5. *Kaiser Wilhelm B between officers Hindenburg and Ludendorff.*

abandon his vague plans for aid to the working classes, as soon as he met the first reactions of the Court. This event caused the displeasure of Russia, which hastened to ally with France in 1891.

The consecutive successions to the position of chancellor that followed, were aimed at drawing up a policy acceptable to both the Reichstag and the ruling classes, which ultimately was not achieved. The political changes required by the rapid industrialization of Germany were hardly promoted. When Bernhard von Bülow was sworn in as chancellor in 1900, he managed to divert attention elsewhere by crafting a truly fascinating foreign policy.

Great Britain was the country that first showed its anti-German sentiments. And was not wrong! Wilhelm sent a telegram in 1896 to South African Democracy president Paul Kruger to congratulate him on the crushing of the English-led Jameson Raid. The German Naval Acts passed in 1897 and 1900 challenged Great Britain's maritime empire. When, in 1904, the British Empire settled its differences with France, the Kaiser -at the suggestion of Bülow- challenged the following year in Tangier the position of France in Morocco, declaring Germany's support for the independence of this French colony.

In 1908, after a visit to England, Wilhelm caused a stir in Germany when he gave an interview to the newspaper "The Daily Telegraph", where he said that a large part of the German people harbored anti-British feelings! There were rumors that he had previously sent the text of the interview to Bülow

Figure 6. *Kaiser Wilhelm B in his military uniform and medals.*

for approval, but he had neglected to read it. This event reduced the Kaiser's role in public affairs and resulted in Bülow being replaced by Theobald von Bethmann Hollweg. Bethmann's efforts to come to an agreement with Great Britain failed. Great Britain would not promise neutrality in a war between Germany and France, except on the condition that Germany would limit her fleet. However, Wilhelm reacted **(Figure 4).**

In other cases again, he proved more prudent and less intransigent. In the Moroccan Crisis of 1911, Germany retreated on its own initiative. If he did the opposite and turned against France to support Morocco, France-German conflict would be inevitable. The foreign policy signed by Wilhelm also contributed to the partnership of the triple alliance between England, France and Russia, the famous *Entente Cordiale*, which he would find in front of him

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Figure 7. *Wilhelm self-exiled in Holland.*

at the outbreak of the Great War in 1914.

Events of Great War

The outbreak of the First World War found Germany ready for war and this was evident from the very first days of the fighting, especially on the West Front. German forces were confronted with those of France, Britain, Belgium and later the USA. The German war machine had enormous advantages. In 1915 it had superior firepower, particularly in howitzer and machine gun fire. The defensive positions were stronger and the army better trained. It even still possessed a large part of Belgium and the industrial regions of France, along with almost all the sources of iron and steel **(Figure 5)**.

Germany missed its only chance of total victory in September 1914. The result was to engage in an unprecedented massacre. During the alternating phases of this devastation, the successes of one side or the other were the occupation of a few meters of ground, excavated from the craters of the eruptions. The trench warfare that followed, went down in history as a sad experience that everyone struggled to forget [7].

During 1916, the great battle of Verdun was raging and, for much of 1917, the British Army was hemorrhaging itself, aiming to demoralize the German army [8]. In 1917, the war with Russia ended with the capitulation of Tsar Nicholas II, which cost him his abdication in March and his assassination, along with his family, in November of the same year. But for the Germans, the main effect was that they were able to throw into the West Front many of the divisions they had used on the East Front in yet another attempt to break through the English-French lines and capture Paris [9].

By the beginning of 1918, it was obvious that the German army was exhausted and the morale of the people had been undermined by the economic blockade. In the course of the war operations, the invention of new methods of exterminating the enemy was developed by both sides. Tanks were perfected. The plane, which the Wright brothers had built only a few years earlier, was first used as a reconnaissance and then to bomb the enemy. Naval aviation turned the navy into a fighting machine, with the construction of the first aircraft carriers and the first seaplanes. German submarines won the battle of the oceans by adopting unorthodox methods as they did not hesitate to torpedo merchant and passenger ships, which enraged the President of USA Woodrow Wilson. Poisonous gases also made their appearance in this war, to justify the immorality of human cruelty [10, 11].

For a few days in the spring of 1918, the easily impressed Kaiser thought that victory was near and triumph was approaching. But the allies had now recovered their courage. While supplies continued to arrive from the USA and the American divisions had already landed on European soil, the end was fast approaching and their victory was beginning to appear.

During the war, although he was nominally commander-in-chief, Wilhelm did not attempt to oppose his generals when they took over the conduct of it themselves. Instead of opposing, he encouraged the grandiose bloodthirsty aims of generals and politicians that precluded any possibility of compromise and peace. When in the fall of 1918 he realized that Germany had lost the war, he did not consider the loss of his throne as a possibility. Despite his initial refusal, he was finally forced to resign on 9 November when he was persuaded to seek asylum in Holland.

Events developed rapidly. At 11 am on the 11th of the 11th month (November) 1918, a ceasefire was ordered on the West Front, for the first time since 1914. Meanwhile, the Ottoman Empire, Austria-Hungary

and Bulgaria had collapsed, while Germany was left alone on the battlefield. Immediately after Wilhelm's departure for Holland, a democratic government was established in Germany with the socialist Friedrich Ebert as president. Ebert was supported by the military, who needed the socialists to deal with communist uprisings. In the end, the Germans accepted the armistice. They were obliged to surrender all their guns, planes and fleet, and withdraw to their borders **(Figure 6)**.

The toll of the war was 8 million dead on the battlefields, while many more succumbed to their injuries, starvation and epidemics. When the German army returned home, President Ebert proclaimed that they had never been defeated. Thus was created, from the very beginning, the myth that Germany had been betrayed by its politicians and that its army was invincible. This was of course a myth, which would soon cause incalculable damage.

In the Hall of Mirrors at Versailles, the leaders of the victorious Entente Cordiale and the defeated Germany signed the famous treaty on June 28, 1919, exactly five full years after Ferdinand's assassination. Wilhelm was absent. According to the *Treaty of Versailles*, Germany was obliged to pay reparations of 226 billion gold marks for the damages it caused, reduce the strength of its army to 100,000 men and its fleet to 108,000 tons. Germany was also obliged to make large territorial concessions. In other words, lost nearly 75,000 square kilometers of its territory, translating to 7 million inhabitants, along with all its colonies. The country's rivers were internationalized, the Rhineland region was demilitarized for the next 15 years, German assets abroad were confiscated, and 90% of the German merchant fleet was handed over to the Allies in return for the damage done to Allied merchant ships during war. In conclusion, Germany was severely limited, both in matters of trade and in military forces and organization. We should not miss the fact that this treaty was one of the causes for the outbreak of the Second World War, exactly twenty years later.

Wilhelm died in exile in 1941, after spending the last years of his life, as a peaceful landowner, in Doorn, Holland **(Figure 7)**.

Conclusions

The outbreak of the First World War was an initiative dictated by petty rivalries, the arrogance of military leaders and the delusions of an easy handling of political and economic disputes in the theater of operations. At the same time, it was signed by Wilhelm, a man with feelings of inferiority, which he struggled to compensate with decisions of greatness and universal supremacy. And while the war began as an attempt to save Austria-Hungary from collapse, it later turned into a world conflict with the blessings of the Kaiser's Germany. Wilhelm, having encouraged the Austrians to pursue an intransigent policy, was afraid when he foresaw the impending war, but he could not stop the mobilization which he had ordered his generals to prepare.

Kaiser often bluntly proclaimed that he was the man who made the decisions. The truth is that the German Constitution of 1871 gave some powers to the Kaiser. This explains the attitude of publicists and British journalists of that time who insisted on presenting him as the man who, more than anyone else, had decided to carry out the war. Nevertheless, over time, historians see Wilhelm as an accomplice rather than the main culprit.

Wilhelm, instead of foreseeing the danger of the inevitable conflicts and using his influence to restrain these appetites, strengthened them himself. Especially with his decision to create a battle-worthy German fleet that would make his homeland proud! Although nimble, well-intentioned and visionary, Wilhelm had the defect of going along with the general stream, rather than resisting and displaying insight and power of judgment [12].

Conflict of interest

The authors declared no conflicts of interest.

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Patient-reported joint status, quality of life, and activity level with the end-stage hindfoot and ankle osteoarthritis

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ABSTRACT

Purpose: To evaluate and associate the preoperative hindfoot/ankle radiographs and the patient-reported outcome measures - PROMs (subjective joint status, quality of life, activity level) prior to hindfoot and/or ankle fusions due to an end stage osteoarthritis (OA).

Methods: In this retrospective analysis, the hospital records of patients admitted for a hindfoot and/or ankle surgery over a 5-year period were reviewed. Inclusion selection identified 144 adults (161 feet) who underwent ankle (ATC), subtalar (ST), talonavicular (TN), and calcaneocuboid (CC) fusion or a combination of thereof. Patients' Foot and Ankle Outcome Score (FAOS), European Quality of life in Five-Dimensions and visual analogue score (EQ-5D-TTO and EQ-VAS), Tegner Activity Scale (TAS) and their preoperative standing radiographs were analyzed and compared across the following subgroups: (a) isolated ATC fusion (ATC_F); (b) isolated ST fusion (ST_F); (c) ATC fusion with concomitant ST fusion (ATC_ST_F); (d) ST fusion with concomitant TN or CC fusion (ST_CONC_F); (e) complete hindfoot (ST + TN ± CC) and ATC joint (ATC_ST_CONC _F) fusion. The patients' PROMs were additionally compared to the general population values.

Results: There was a marked subjective ankle dysfunction (average FAOS cumulative – 40) decreased quality of life (average EQ-5D-TTO – 0.41, average EQ-VAS – 56) and activity level (mean TAS – 2) across all the patients' subgroups in comparison to the general population (FAOS cumulative – 87, EQ-5D-TTO – 0.81, EQ-VAS – 80, and TAS – 5). Analysis within the subgroups revealed a significant difference between: ATC_F and ST_CONC_F in FAOS Symptoms (36 vs. 55); ATC_F and ST_F in EQ-5D VAS (61 vs. 50) and TAS (2 vs. 3). Multivariate linear regression models revealed a significant negative correlation between older age, female gender, higher levels of radiographic OA in ATC and Chopart joints, and longer symptom duration toward some of the preoperative PROMs

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Conclusion: Patients suffering from an end-stage hindfoot or ankle OA experience a profound deterioration in subjective ankle function, quality of life, and activity levels. Older age, female gender, longer symptoms duration, and higher levels of radiographic OA in ATC or Chopart joints were the negative predictors for their preoperative PROMs.

KEYWORDS: Ankle; Hindfoot; Osteoarthritis; Fusion; Subjective joint status; Quality of Life; Activity level

Introduction

Hindfoot and ankle injuries are among the most common musculoskeletal injuries in the population, with an incidence of 1/10.000 per day (1). In approximately 40% of cases, chronic dysfunction develops (2), leading to posttraumatic osteoarthritis (OA) in the long term. Posttraumatic OA accounts for nearly 70-90% of all hindfoot and ankle OA cases, followed by rheumatoid arthritis (12%) (3). Primary OA is rare and accounts for only 7% of all hindfoot and ankle OA (3). OA of the hindfoot and ankle results in significant impairment of joint function (4), quality of life (4), and physical performance (5).

Clinical examination along with native weight bearing and radiographs in anterio-posterior, lateral, and Mortice views are sufficient to evaluate OA of the hindfoot and ankle (6). Patient-reported outcomes (PROMs) can provide additional insight into subjective hindfoot and ankle status (7-9). Routine physical examination includes careful inspection of the entire hindfoot and ankle, assessment of alignment and stability, and measurements of range of motion (10). Clinical examination of the OA of the hindfoot and ankle often reveals pain, stiffness, limited range of motion, chronic swelling, alignment deformities, etc (3). The ankle joint (articulatio talocruralis - ATC), subtalar joint (ST), talonavicular joint (TN) and calcaneocuboid joint (CC) are considered separately and assessed using OA criteria on native weight bearing radiographs (11,12). The modified Kellgren-Lawrence score is most commonly used to assess ATC osteoarthritis, whereas osteophyte formation and joint space narrowing are more appropriate for assessing ST, TN, and CC joint OA (10,12).

The aim of this study was to evaluate and correlate the preoperative radiographs with the subjective ankle joint-specific dysfunction, general quality of life, and activity level in patients with the end-stage ankle or hind-foot OA prior to the surgical intervention (fusions of ankle, subtalar, Chopart joints, or the combination of thereof). The gathered PROMs were additionally compared to the values of the general population.

Materials and Methods

Study design

The study was designed as a retrospective analysis of patients' data collected from adults, who were scheduled for an ankle or hind-foot fusion due to an end-stage OA at a national university orthopedic center. The investigational plan was approved by the National Medical Ethics Committee (No. 0120-99/2019/4). Hospital records of 275 patients admitted for elective hindfoot and/or ankle surgery between January 2015 and December 2020 were reviewed. In a further selection, 144 patients, 18 years or older, with ATC, ST, TN and/or CC OA and subsequent fusion were included in this study. Concomitant procedures such as corrective osteotomies, ligament repair, and Achilles tendon lengthening and tendon transfers were allowed and recorded. All included patients had clear clinical and radiological evidence of high-grade OA of the ankle or the hind-foot. Previous conservative treatment attempts had been exhausted and had led to unsatisfactory results.

Patient data

Of the 144 patients, 17 had bilateral surgery. Each

A) Subtalar fusion

PreOP radiographs
KL_ATC: 1
Osteophy + JSN ST: 4
Osteophy + JSN Chopart: 2

Preoperative PROMs
FAOS Cumulative: 45
EQ-5D-TTO: 0.32
EQ-VAS: 40
TAS: 4

B) Ankle fusion

PreOP radiographs
KL_ATC: 4
Osteophy + JSN ST: 2
Osteophy + JSN Chopart: 2

Preoperative PROMs
FAOS Comulative: 42
EQ-5D-TTO: 0.41
EQ-VAS: 65
TAS: 2

Figure 1. *Standing ankle/hindfoot radiographs and PROMs of two representative patient cases. One was scheduled for ST fusion (A) and the other one for ATC fusion (B).*

OA, osteoarthritis; PreOp, preoperatively; PostOp, postoperatively; KL_ATC, ankle Kellgren-Lawrence criteria; Osteophy, Osteophyte formation; JSN, joint space narrowing; ST, subtalar joint; FAOS, Foot and Ankle Outcome Score; EQ-5D, EQ-5D-3L-TTO, European Quality of Life in Five Dimensions; TTO, 3-level time-trade-off; VAS, visual analogue scale; TAS, Tegner activity scale.

foot was considered as a separate entity, therefore 161 cases (feet) were included in the study. Five groups were formed according to the procedures performed: (a) isolated ATC fusion (ATC_F); (b) isolated ST fusion (ST _F); (c) ATC fusion with concomitant ST fusion (ATC_ST_F); d) ST fusion with concomitant TN and/or CC fusion (ST _CONC_F); e) complete hindfoot (ST + TN ± CC) and ATC joint fusion (ATC_ST_ CONC _F). Patients' demographic data (age, gender, BMI), medical history (smoking

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TABLE 1.

Patient demographics, medical history, symptoms durations and radiographic OA parameters.

	ATC_F (N = 40)	ST_F (N = 42)	ATC_ST_F (N = 19)	ST_CONC_F (N = 60)	ATC_ST_CONC_F (N = 0)
Gender (male/female)	27 / 13	25 / 17	13 /6	21 / 39	n.a.
Age (years)	53 (14)	51 (15)	60 (10)	55 (14)	n.a.
BMI (kg/m2)	30 (6)	29 (4)	29 (5)	30 (5)	n.a.
Symptoms duration (years)	11 (9)	10 (9)	6 (5)	9 (8)	n.a.
Smoking (yes/no)	11 / 29	12 / 30	3 / 16	15 / 45	n.a.
OA_ATC (Modified KL)	4 (1)	2 (1)	4 (0)	2 (1)	n.a.
OA_ST (Osteophytes + JSN)	2 (1)	3 (0)	2 (1)	3 (0)	n.a.
OA_TN_CC (TN + CC Osteophytes + JSN)	1 (0)	2 (1)	3 (2)	2 (1)	n.a.

ATC_F, ankle joint fusion; ST_F, subtalar joint fusion; ATC_ST_F, ankle and subtalar joint fusion; ST_CONC_F, subtalar, talonavicular and/or calcaneocuboid joint fusion; ATC_ST_CONC_F, complete fusion of the hindfoot and ankle joint,; BMI, body mass index; KL, Kellgren-Lawrence; OA_ATC, osteoarthritis of the ankle; OA_ST, subtalar joint osteoarthritis; OA_TN_CC, osteoarthritis of the talonavicular and calcaneocuboid joint.

habits) and duration of their symptoms were recorded, details given in Table 1. Two representative cases of pre-operative radiographs and PROMs are demonstrated in Figure 1.

Patient evaluation and radiological analysis

Three patient-reported outcome measures (PROMs), Foot and Ankle Outcome Score (FAOS), European Quality of Life in Five Dimensions (EQ -5D) and Tegner Activity Scale (TAS), were distributed and completed before the surgery on admission to the hospital. FAOS and TAS have been double translated and have been used in several previous studies for the Slovenian population (18,19). EQ -5D has been validated for the Slovenian population (14).

1) Foot and Ankle Outcome Score (FAOS): The Knee Injury and Osteoarthritis Outcome Score (KOOS) was modified to capture problems related to the foot and ankle. The FAOS assesses 5 patient-related subdomains; Pain (9 items), Symptoms (7 items), Activities in daily living (ADL) (17 items), Sport/Recreation (5 items) and quality of life related to foot and ankle (QoL) (4 items). Combined, they form the FAOS Cumulative score. The score for each subdomain and the FAOS Cumulative score are calculated and normalized to a scale of 0 to 100, where 100 indicates no foot- or ankle-related symptoms (7). The mean (SD) FAOS scores determined by Golightly et al. (13) in a community-based study are as follows: FAOS Cumulative 87 (11), FAOS Symptoms 87 (16), Pain 86 (20), ADL 95 (10), Sport 74 (34), and QoL 83 (23).

2) European Quality of Life in Five Dimensions (EQ -5D): consists of a descriptive system (EQ -5D-3L) and a vertical visual analogue scale (EQ-VAS). The descriptive system is comprised of 5 domains

TABLE 2.

Pre-operative patient reported joint-specific patient outcome measures sorted according to surgical procedure and intercompared using a one-way ANOVA with Turkey post-hock correlation test.

	ATC_F (N = 40)	ST_F (N = 42)	ATC_ST_F (N = 19)	ST_CONC_F (N = 60)	ATC_ST_CONC_F (N = 0)	p
FAOS Cumulative	43 (17)	42 (13)	32 (17)	42 (17)	n.a.	0.119
FAOS Pain	42 (18)	44 (15)	36 (18)	43 (21)	n.a.	0.578
FAOS Symptoms	36 (10)*	46 (15)	37 (21)	53 (19)*	n.a.	0.000*
FAOS ADL	55 (20)	51 (17)	39 (21)	48 (20)	n.a.	0.057
FAOS Sport	24 (28)	19 (19)	10 (16)	18 (19)	n.a.	0.190
FAOS QoL	25 (18)	17 (13)	12 (12)	20 (18)	n.a.	0.059
EQ-5D-3L-TTO	0.44 (0.11)	0.36 (0.17)	0.42 (0.13)	0.43 (0.17)	n.a.	0.275
EQ-5D VAS	63 (21)*	50 (17)*	57 (16)	52 (18)	n.a.	0.049*
Tegner Activity Scale	2 (0-5)*	3 (0-5)*	2 (0-7)	2 (0-5)	n.a.	0.008*

*FAOS, Foot and Ankle Outcome Score; ADL, Function, activities of daily living; QoL, quality of life; EQ-5D-3L, European Quality of Life in Five Dimensions; TTO, 3-level time-trade-off; VAS, visual analogue scale; ATC_F, ankle joint fusion; ST_F, subtalar joint fusion; ATC_ST_F, ankle and subtalar joint fusion; ST_CONC_F, subtalar, talonavicular and/or calcaneocuboid joint fusion; ATC_ST_CONC_F, complete fusion of the hindfoot and ankle joint. Statistically significant differences between procedures by Tukey post-hock test are marked with *.*

(mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with 3 levels: none (1), some (2) and extreme problems (3). Together, the 5 dimensions form a 5-digit number that is converted into a utility index reflecting the individual's level of self-rated health (8). A country-specific, time-trade-off-based EQ -5D 3-level (EQ -5D-3L-TTO) value was established to determine the index numbers corresponding to the 5-digit score of patients' health states (14). EQ-VAS is a vertical scale reflecting patients' self-rated health from worst (0) to best imaginable (100). EQ-5D-TTO is the most commonly used questionnaire to assess quality of life. The average EQ -5D-TTO utility index score in the general Slovenian population is 0.81, and the average VAS score is 80 (15).

3) Tegner Activity Scale (TAS): measures patients' activity on a scale from 0 (disability) to 10 (professional football: national or international level) (16). Recently, it has been proposed to use TAS for evaluation of activities related to foot and ankle and other joints (9). Briggs et al. (17) reported the mean scores of TAS, divided into age groups for the general population. The median value for people aged 46 years and over, which includes the majority of our patients, was 5.

Native foot and ankle radiographs were analyzed for: ankle OA (modified Kellgren-Lawrence criteria, 0-4) (12); ST joint OA (osteophyte formation (0-3) and joint space narrowing, (0-3)) (11,12); and TN + CC joint - Chopart joint osteoarthritis (osteophyte formation (0-3) and joint space narrowing (0-3) - combination of both entities of each joint) (11). The data are shown in Table 1.

Statistical analysis

Descriptive statistics for patients' demographics, medical history and radiological OA status were used for all 161 cases. Numerical data are presented as mean values (SD), number of cases is given for categorical variables. TAS is presented as medians (min-max). The T-test for unpaired samples was used to compare the values of patient-reported outcomes before surgery with those of the general population (GP) (13,15,17). A one-way ANOVA and Tukey HSD post-test were used to test for significant differences between the five groups. Associations between predictors and preoperative scores of PROMs were investigated with linear regression models. Statistical analyses were performed using SPSS software (version 23.0; IBM, Chicago, IL, USA). The level for statistical significance was set at $p < 0.05$.

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TABLE 3.

Results of the multivariate linear regression models for the correlation between the predictors and the pre-operative values of the patient-reported outcome measures.

Dependent variable	R2	Predictors	B	p	CI Lower	CI Upper
FAOS Cumulative	0.067	Age	-0.260	0.012	-0.566	-0.070
FAOS Pain	0.113	Gender KL_ATC	-0.262 -0.255	0.011 0.013	-17.217 -7.569	-2.270 -0.906
FAOS Symptoms	0.081	KL_ATC	-0.285	0.006	-7.304	-1.271
FAOS ADL	0.131	Age Symptoms duration	-0.322 -0.200	0.002 0.047	-0.784 -0.927	-0.188 -0.006
FAOS Sport	0.121	Age	-0.347	0.001	-0.881	-0.243
FAOS QoL	n.a.	/	n.a.	n.a.	n.a.	n.a.
EQ-5D-3L-TTO	0.079	Symptoms duration	-0.281	0.007	-0.009	-0.002
EQ-5D VAS	0.158	Symptoms duration OA_chop	-0.337 -0.211	0.001 0.033	-1.216 -2.925	-0.330 -0.127
Tegner Activity Scale	0.161	Gender	-0.348	0.001	-1.798	-0.507

FAOS, Foot and Ankle Outcome Score; ADL, Function, activities of daily living; QoL, quality of life; EQ-5D-3L-TTO, European Quality of Life in Five Dimensions 3-level time-trade-off; CI, confidence interval. Only statistically significant predicting variables are reported ($p < 0.05$).

Results

Preoperative PROM scores indicated significant ankle dysfunction, impaired quality of life and activity levels in all patients with the end-stage of hindfoot or ankle OA. All FAOS subscales were significantly below the normative values of the general population: FAOS Cumulative 32 (ATC_ST_F) - 43 (ATC_F) vs. 87 (GP) ($p < 0.000$), Symptoms 36 (ATC_F) - 53 (ST_CONC_F) vs. 87 (GP) ($p < 0.000$), Pain 36 (ATC_ST_F) - 44 (ST _F) vs. 86 (GP) ($p < 0.000$), ADL 39 (ATC_ST_F) - 55 (ATC_F) vs. 95 (GP) ($p < 0.000$), Sport 10 (ATC_F) - 24 (ATC_ST_F) vs. 74 (GP) ($p < 0.000$), and QoL 12 (ATC_ST_F) - 25 (ATC_F) vs. 83 (GP) ($p < 0.000$). Patients with ATC_ST_F had the lowest scores in the majority of FAOS subscales. The one-way ANOVA test revealed a significant difference between ATC_F and ST_CONC_F in FAOS symptoms ($p < 0.001$). The highest suppression of EQ-5D-3L-TTO scores was in ST_F (0.36) and the lowest in the ATC_F (0.44), with no significant differences between groups. The same pattern of value reduction was observed at EQ-5D VAS, amid ST_F (50) and ATC_F (63), with a statistically significant difference between the two ($p < 0.049$). Patients' with ATC_F had the highest scores in EQ-5D-3L-TTO and EQ-5D VAS. All EQ-5D-TTO and VAS values were significantly lower compared to the general population; EQ-5D-TTO 0.36 (ST_F) - 0.44 (ATC_F) vs. 0.81 (GP) ($p < 0.000$), EQ -5D VAS

50 (ATC_F) - 62 (ST_F) vs. 80 (GP) ($p < 0.000$). Tegner values were likewise statistically lower in the observed groups compared to the general population, 2 (ATC_F, ATC_ST_F, ST_CONC_F) - 3 (ST_F) vs. 5 (GP) ($p < 0.000$). Additionally, statistically significant difference was noted amongst ATC_F and ST_F ($p < 0.008$), with ST_F patients being the most active. See Table 2 for details.

Multivariate linear regression models revealed a significant negative correlation ($p < 0.05$) between older age, female gender, higher Kellgren-Lawrence ATC values, higher OA of the Chopart joint and longer symptom duration toward certain preoperative PROMs. Older age was negatively correlated with preoperative FAOS Cumulative, ADL and Sports. Longer symptom duration was negatively correlated with FAOS ADL, EQ-5D-3L-TTO and EQ-5D VAS. There was also a negative correlation between higher OA of the Chopart joint and EQ-5D VAS. Higher Kellgren-Lawrence ATC values were negatively correlated with FAOS Pain and Sport, while female gender had a negative correlation with FAOS Pain and Tegner Activity Scale. These data are presented in Table 3.

FAOS, Foot and Ankle Outcome Score; ADL, Function, activities of daily living; QoL, quality of life; EQ-5D-3L, European Quality of Life in Five Dimensions; TTO, 3-level time-trade-off; VAS, visual analogue scale; ATC_F, ankle joint fusion; ST_F, subtalar joint fusion; ATC_ST_F, ankle and subtalar joint fusion; ST_CONC_F, subtalar, talonavicular and/or calcaneocuboid joint fusion; ATC_ST_CONC_F, complete fusion of the hindfoot and ankle joint. Statistically significant differences between procedures by Tukey post-hock test are marked with *.

Discussion

The most important findings of this retrospective study were: a) patients suffering from an end-stage hindfoot or ankle OA experience a profound deterioration in subjective ankle function, quality of life, and activity levels, older age, female gender, longer symptoms duration; b) higher levels of radiographic OA in ATC or Chopart joints were the negative predictors for their preoperative PROMs.

Of all patients included in our study, those with ATC and ST OA had the lowest FAOS scores, followed by isolated ATC osteoarthritis. The statistically significant decline ($p < 0.001$) in relation to the general population was 50-60%. Similar observations were also made in a cross-sectional study by Kolar et al. (18) comparing PROMs from seven different ankle pathologies (osteoarthritis of the ATC, recurrent osteochondral lesion of the talus (OLT), primary OLT, lateral instability, anterior impingement, posterior impingement and combined impingement). They observed a 50% decline in patient-perceived ankle pain, symptoms and daily activities with additional deterioration of nearly 25% in sport/recreational activities and joint-specific quality of life in patients with ATC osteoarthritis compared to the general population. A large reduction (about 50%) in all PROMs in patients with ankle OA was also acclaimed by Waly et al. (20), but using different questionnaires (Ankle Arthritis Score, Ankle Osteoarthritis Scale, Mental Components Score and Physical Components Score). This indicates the great importance of ATC OA for hindfoot and ankle function.

The values of EQ-5D-TTO and EQ-VAS were lowest in patients scheduled for an ST fusion (0.36 and 50, respectively). This implies that quality of life is lowest in patients with ST OA, which contradicts the FAOS results. However, the differences between the five groups were small, not statistically significant in EQ-5D-TTO ($p < 0.275$) and only a weak difference was found in EQ-5D VAS between patients with ATC and ST osteoarthritis ($p < 0.049$). Taking into account that EQ-5D VAS is considered less accurate apropos EQ-5D-TTO in assessing ankle quality of life (21), and the weak statistical significance, we can conclude that the differences between the five groups are negligible. Nevertheless, the absolute preoperative scores (0.36-0.44) show a strong deterioration compared to the general population (15), they are in line with previous studies (22) and are in equivalent with those reported in knee (0.49) and hip (0.52) osteoarthritis (23), demonstrating the severe impact of this pathology on quality of life.

Tegner activity values were statistically significantly decreased in all five groups ($p < 0.001$) toward general population. The least profound decrease was in patients suffering from ST OA, who on average were still able to hike or backpack (level 3), while patients in the other four groups were on average only able to take shorter walks on uneven ground (level 2). This intergroup difference was also statistically significant ($p < 0.008$). Patients with ST OA tend to be the most active, but also have the lowest EQ-5D-TTO and EQ-VAS scores. This gives the impression that isolated ST OA is less disabling and allows patients to engage in more demanding activities, which ultimately result in more severe pain and a lower life quality. Low preoperative values of TAS in patient with ATC and hindfoot OA were also reported by Hanna et al (24). The mean value of TAS in 61 patients who had high-grade ATC osteoarthritis was level 1 (sedentary work, walking on even ground). We must emphasize that TAS was primarily designed to assess knee sports injuries and is hence less sensible for other pathologies. There is also a wide discrepancy of mean values in the general population, ranging from level 3 to level 6 (17,25). In view of all this, the values obtained in the hindfoot and ankle must be interpreted with some caution.

Higher age, higher Kellgren-Lawrence ATC scores, higher OA of the Chopart joint, female gender, and longer symptoms duration were negatively correlated with the preoperative PROMs. There are very limited data on the predicting factors for the preoperative scores on patient-reported outcome measures in the current literature. Similar negative predictors of hindfoot and ankle pathology were reported by Brulc et al. (19) in patients with osteochondral lesions of the talus. They found a negative correlation between female gender, higher BMI and higher radiographic ankle OA toward preoperative FAOS scores. While the influence of age and longer symptom duration (chronification of pain) as well as poor cartilage status (OA-related pain) on preoperative ankle subjective status is comprehensible, the influence of gender is less clear. Nevertheless, a similar trend towards lower PROMs in women has been reported in other studies (19,26,27). A partial explanation was provided by Fillingim at al. (28) in a large meta-analysis in which they found higher pre- and post-operative pain scores in women, involving several endogenous and exogenous pain modulation mechanisms that are not yet fully understood.

The following limitations of this study need to be considered: First, it was a non-randomized and unblinded case series, however it represents a real clinical situation of the whole patient series treated over twelve years in a tertiary orthopedic university center. Second, the hindfoot and ankle share loading and function as a whole. Projection of pain is common, so separate assessment of each component may be difficult and less reliable. Moreover, only a preoperative assessment of the hindfoot and ankle was performed with standard ankle-specific and general quality of life questionnaires. Follow-up with the same set of PROMs is essential for a better and more thorough analysis. Thirdly, there is always a possibility of subjective bias when analyzing radiographs. Much emphasis has been placed on standardizing the digital measurement protocols to minimize the variability.

Conclusions

Patients suffering from an end-stage OA of the hindfoot and ankle suffer from profound impairment of joint function, quality of life and activity levels. Impairment of joint function is most severe in patients with ATC and ST joint OA, while quality of life and activity levels are equally impaired in all five groups. Moreover, older age, female gender, higher Kellgren-Lawrence ATC OA scores, higher Chopart joint OA scores and longer symptoms duration are negatively correlated with the preoperative PROMs.

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ACTA REVIEW
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School scoliosis screening, a program useful not only for the prevention of scoliosis. Part one: historical data, policies of administration, clinical and practical considerations, setting up a school scoliosis screening program and an effective protocol.

Theodoros B. Grivas

ABSTRACT

This report presents an introduction and brief historical data about the school scoliosis screening programs (SSS) and the universal policies for its administration. The clinical and practical considerations/topics for setting up and running the SSS programs for any SSS program examiner are described and analyzed. A protocol is proposed to implement a SSS program. The parameters of the proposed protocol are presented and analyzed, explaining why these specific parameters are included. This protocol may hopefully be used by other interested in SSS orthopaedic teams for the in-depth study of idiopathic scoliosis (IS).

KEYWORDS: School scoliosis screening - SSS, history, administration, clinical considerations, practical considerations, setting up SSS, protocol, anthropometry, Adam test

A. Introduction and brief historical data.

The currently implemented School Scoliosis Screening (SSS) programs aim to the prevention of idiopathic scoliosis (IS). The original and main aim of SSS is to identify most or all the individuals with *truncal asymmetry (TA)* and / or unrecognized IS at an early stage when a less invasive treatment is more effective, in other words it is prevention! The preventive examination for scoliosis in the general health assessment programs of youngsters and especially of school children started in Europe from the beginning of the 20th century. In Greece the school doctors were also assessing the children for scoliosis as well. There is evidence that these programs were implemented in many European countries and cities, also in Greece, and documented in a booklet named «Η ΣΚΟΛΙΩΣΙΣ», published in Athens 1915, written Dr Em. Lambadarios, and published by Thanos Tzavelas, (Fig. 1). The mentioned cities and countries were Hamburg, Lausanne, Paris, Athens, and Sweden.

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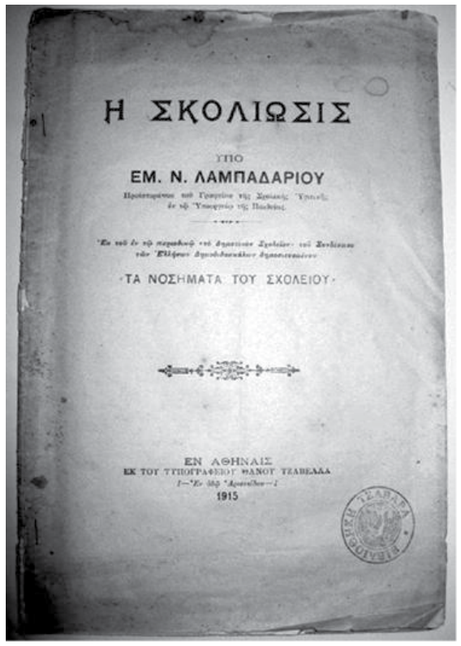
Fifty years later, in 1963, SSS began in Aitken, a town in Minnesota, organized by Dr. Lonstein. Dr Lonstein stated that by the screening the benefits are great. The curves are detected when they are small, allowing progressive deformities to be detected early, promptly braced and deterioration prevented. The need for future surgical correction is thus decreased. The routine screening in Minnesota of school children for spine deformities has proved to be an effective method for the early detection of spine deformities. For the SSS programs Dr Lonstein stated that "The screening test is rapid and easy -"a 30-second investment for a lifetime of dividends", [1,2,3]. Dr. Dean MacEwen, was also involved in the early development of voluntary SSS programs by implementing them in schools in the state of Delaware in the 1960s, [4].

In 1975 Dr. Panagiotis Smyrnis organized and conducted the first SSS in Athens, Greece. In Attica 3494 children from 12-14 years of age were examined visually, conducting the Adam test. The percentage of clinically positive were found to be 10% and the percentage of radiologically positive of confirmed scoliosis for curves of 10 degrees or more, was 4.6% for girls and 1.1% for boys. This study also found that children with blond hair and blue eyes are more prone to scoliosis, compared to children with dark features. Dr Smyrnis noted that the bending test is still the most common, because it is simple and easy to use even for non-experts, but also a second check before any radiological examination is needed, and also in a calm environment. He stated that "it should be emphasized that apart from the size of the hump, its position in the spine has a clinical significance". Moreover, he recommended that the most critical age for mass screening is from 10-13 years old, when 85% of clinically significant IS appear, and it is observed usually 3:1 ratio between clinically and radiologically positive children, [5,54]. The results of this program were initially presented at the 3rd "N. Giannestra" Symposium in September 1975, and this program's outcomes publications followed, [55,56,57]. Consequently, similar SSS programs were implemented by interested by SSS orthopaedic teams in many Hellenic cities.


Η ΣΚΟΛΙΩΣΙΣ

ΥΠΟ

ΕΜ. Ν. ΛΑΜΠΑΔΑΡΙΟΥ

ΤΑ ΝΟΣΗΜΑΤΑ ΤΟΥ ΣΧΟΛΕΙΟΥ

ΕΝ ΑΘΗΝΑΙΣ
ΕΚ ΤΟΥ ΤΥΠΟΓΡΑΦΕΙΟΥ ΘΑΝΟΥ ΤΣΑΒΕΛΛΑ
1915

*Figure 1. [***ΕΜ. Ν. ΛΑΜΠΑΔΑΡΙΟΣ Η ΣΚΟΛΙΩΣΙΣ***. ΤΑ ΝΟΣΗΜΑΤΑ ΤΟΥ ΣΧΟΛΕΙΟΥ. ΕΝ ΑΘΗΝΑΙΣ. Εκ του τυπογραφείου Θάνου Τζαβέλλα , Εν οδώ Αριστείδου 1, 1915.]*

The "Thriasio" and "Tzaneio" Hospital SSS program was conducted during 1996-2009 and 2009-2019 respectively. During this period the author of this report was servicing the Hellenic National Health System, and 24.223 children were examined. Further information on the history and reported outcomes of Hellenic SSS programs up to 2000, is provided in the book entitled: "School Screening in Greece", [5].

B. Policies of Administration of SSS programs.

The worldwide encouraging and adverse polices for implementation of SSS programs vary, [6,7]. The role of the US PREVENTIVE Services Task Force (USPSTF) has initially been negatived for years regarding the school screening implementation, [8,9]. Recently there is a universal tendency of a pro-SSS programs implementation, including the USPSTF as well. The USPSTF in its more recent report conclud-

ed that screening can detect adolescent idiopathic scoliosis, (AIS). Bracing and possibly exercise treatment can interrupt or slow progression of curvature in adolescence, [10]. Currently it seems that the pendulum swings back to scoliosis screening, [11].

For the set-up of our SSS program, the hospital administration applied to the Greek Ministry of Education for obtaining permission to examine the children in the school setting. The Ministry of Education sent a circular to Elementary and High Schools with its positive permission recommending the examination. The School Principal was provided with the educational material about our SSS program by a screening team member and the teachers distributed the consent letter, prepared by the SSS team, for the parents who were requested to sign for their children to be examined. In case of a scoliometric documented TA of the examinees, asymmetry indicating re-examination, the team prepared an invitation/referral letter of the SSS program for re-examination of the child or adolescent in the scoliosis clinic of the hospital. The examinees presented this letter to their parents.

The examination team usually consists of well-trained to implement SSS programs Orthopaedic doctors, Physiatrists, General Medicine doctors, Health visitors, Nurses, and Physiotherapists.

The financial information for the SSS programs, which must be used by the national decision-makers administrators, should be based on the studies of the direct cost of the program. The direct cost of a SSS program can be reduced to a minimum if it is well organized and carried out on a voluntary basis, [12].

Our training center for certified examiners for the SSS programs and our SSS program was legislated by the Hellenic State, see ΦΕΚ Αρ. Φύλλου *4168, Τεύχος B, 30/11/2017*, based on the "Special Training Center for the Implementation of the Student Screening Program for Scoliosis and Other Spinal Deformities".

C. Setting up SSS programs: Clinical and practical considerations

The training programs must include three trajectories. The first is the theoretical education on the spinal anatomy, physiology, pathology and treatment related to scoliosis and other spinal deformities. The second is the involvement in the performance of the SSS program. The third is the attendance of the scoliotic clinic in hospital, where the referred children are re-examined.

Before the involvement in any SSS program the examiners must be trained and certified in an official certification training center and must be familiarized into the following topics, [12].

1. How to obtain permission from the a) Administration of the Hospital, and b) the Ministry of Education to perform SSS.

2. How the groups of examiners are organized. The team includes orthopaedic surgeons, health visitors, physiotherapists, school nurses where available.

3. The instruments/forms on which the team must be appropriately trained for the implementation of the SSS.

4. Familiarization and training in confronting the behavioural issues of the children and adolescent age groups (children in primary and secondary education).

5. Methods for communicating with the School Administration, which is significant for the success of the SSS.

6. Management of the "materials" including the various forms to fill (protocol, consent and re-examination, at the scoliosis clinic, letters), and how to examine the children and use the relevant instruments, including the scoliometer, the body weight scale and the height measurement apparatus.

7. The decision making for the time and the screening frequency and performance, which is variable, depending on many parameters (e.g. how to schedule the screening in order to minimally disturb the educational program of the children).

8. Management of the data collection, its processing and analysis.

9. How children are monitored (those asymmetric children at risk of developing scoliosis or scoliotics), including referral to the outpatient clinic for re-assessment and the onset of early non-operative (conservative) treatment.

10. Increasing the community's awareness and insight into scoliosis by presenting and publishing data collected through SSS programs, [13].

Discussing the item 9 of the above list we note the following facts. The main burden of discontinuation of various school screening programs internationally was the phenomenon of over-referrals from SSS programs and of the ongoing controversy over its application. The over-referrals in the scoliosis clinics are mainly included in the *false positives* group, that is the children clinically diagnosed having a probable scoliosis due to existence of a hump, found conducting the Adam's test. This creates unjustified stress to the family and the child, but also unjustified transport expenditures for the visit to the scoliosis clinic and loss of the working day and wage for the parents. However, the real problem is the *false negative* cases, that is children who missed the opportunity for early diagnosis. This can be minimized by a certified skilled examination team which should always use the scoliometer, [14]. The amount of scoliometric TA by age for recommending re-examination, is discussed well along this report.

As far as the burden created by the *false positive* referrals is concerned, we note the following: It must be widely accepted that, with SSS programs, a chance is mainly given to the school-aged population to rule out those who will be at risk for developing scoliosis, rather than discover those who definitely have scoliosis, and it is easy to diagnose. This is especially true if there is a significant surface deformity justifying the central axis (that is the spinal) deformity. There is something else that must be highlighted and clearly understood. The SSS program aims at detection of surface deformity and/or the existing number of scoliosis cases; it does not aim at predicting which scoliotic curves will create deformity that will require some type of conservative or surgical treatment. The criteria used to predict deterioration of a small or moderate curve are unfortunately not related to SSS programs. All asymmetric children, therefore, who will be entitled to develop scoliosis, [15], will miss the opportunity to be picked up and will probably be discovered too late, when surgery will be the only treatment option. As expected, the outcome will be particularly worse in poor societies. Therefore, in explaining the role of school screening, it must also be clearly understood that its cost must be the direct cost of performance of the actual screening program and not the subsequent expenditures of follow-up, radiographs and other modalities described in the current literature, [12, 16].

Finally, the fact that the SSS programs were in some places discontinued was the result of a triumph of epidemiology over early diagnosis, and this in reality is a disaster, [6, 58]. Prevention must be a standard policy in civilized societies with medical systems caring about people's wellbeing and not about statistics, epidemiology or only cost. We always have to remember what the axiom in ancient Greece, the cradle of western civilization was. Ancient Greeks used to say that "metron of everything is man"; the measure, in other words, of appraising everything is only the human being, nothing else.

D. The Protocol.

In Table 1**,** the form for the study of school population of our used scoliosis screening protocol is presented. This SSS protocol is mostly original. A few commonly used parameters based on the existing peer-review literature are included, (mainly the scoliometer readings) and collection of other parameters based on our experience running our SSS program for twenty-five consecutive years.

In this SSS protocol form, initially the geographical region of the school is written and the date of the examination of each child. This information is useful because in the analysis of the results the place and the possible role of this geography on the prevalence of scoliosis is documented. It is reported that the prevalence of scoliosis depends to the geographical latitude, [17].

The date of the examination may be used not only for the documentation of the time of SSS implementation but also by using the documented date of birth, we can calculate the exact age of the examinee, a very important parameter for the study of IS.

D-a. The Personal Demographic Data are collected.

The surname and the name of the examinee, the father's and mother's name are written. In case that

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two children have the same name (synonymy), this information makes it possible to avoid mistakes and the use of the wrong data.

The home address of the examinee, (street, number, city and telephone number), provide a lot of convenience to the SSS team in case any communication with the family is necessary for referral and reexamination in the scoliosis clinic or for any other medical reason.

The school type and name (primary, high School, etc.) and the grade of the examinee is also useful information. The knowledge of the type of the school is very important. For example, in a specialized school for children suffering visual deficiency, the prevalence of scoliosis is quite different from that of children attending the ordinary public or private schools, [18].

D-b. The family demographic Basic Data are documented.

The birth place of the examinee and his/her date of birth (DoB), the father's and mother's birth place, age in years and profession are documented. All this information is offering very important data related to epigenetic factors affecting the prevalence of idiopathic scoliosis, [19,20,21,22,23].

D-c. Biological and somatometric data.

The following parameters are always measured and recorded as a mandatory part of the SSS program. The sex (male or female). It is well reported that the adolescent idiopathic scoliosis (AIS) affects mainly the females, (almost 80%), [24].

In girls we also document the exact age at menarche, (day, month, year). This information is very important because if an examined girl has truncal asymmetry, she is candidate or suspicious for developing scoliosis or she has already started developing scoliosis. The age of menarche is one of the parameters that dictate the treating physician how to tailor the proper management for her. Younger non-menarchial girls may develop progressive deformity while post-menarchial older girls have a reduced likelihood for progression. Additionally, a significant difference was found between menarche positive and menarche negative scoliotic girls in relation to the laterality of scoliotic curves: The former showed predominantly right sided primary curves while the latter had mainly left primary curves, [25].

The standing and sitting body height in cm is measured using the standard height measuring device. The assessment of standing body height and the stratification of this measurement by age in the examined children will allow us the appraisal of growth of the examinees and compare it with various internationally reported publications. This may provide some aetiological clues for the AIS. The sitting body height is one useful parameter, an indicator of spinal growth, [26, 27].

The measurement of body weight in Kg follows. It is reported in the literature that the scoliotic girls are slimmer with lower BMI and higher that the aged matched non-scoliotic children, [28, 29, 30, 31, 32].

The type of the gait, namely in-toeing, out-toeing, neutral type, is recognized by asking the examinee to walk. This information is looked-for, based on the knowledge that the scoliotics were found to have femoral anteversion asymmetry. Prochiantz 1986, studied the femora of 8 patients with idiopathic scoliosis using CT and concluded that a number of such cases originate in asymmetric femoral anteversion. Burwell et al 1988, using an ultrasound method to measure femoral anteversion, found that anteversion asymmetry was greater in school screening referrals and their siblings than in controls. A derivative also of femoral anteversion and its asymmetry (residual functional anteversion) was related to the Cobb angle of the lowest lateral spinal curves of 20° or more, [33, 34, 35, 36].

The eyes' color (dark, bright (green or blue), is documented as a non-mandatory note. Frequently AIS children have bright color eyes, [5]. However blue eyes may reveal syndromic scoliosis as at Waardenburg syndrome, which is characterized by the association of pigmentation abnormalities, including depigmented patches of the skin and hair, vivid blue eyes or heterochromia irides, and sensorineural hearing loss, [37, 38].

The handedness (right or left-hand dominance, or both) of the children is assessed. The hand preference of children is documented by just asking them which hand they prefer for everyday activities, especially writing, eating, throwing an object or performing fine motor skills. For those children where hand preference for performing different types of manual tasks vary, hand preference is determined by the number of performed tasks by each hand. Thus, the examiners have a clear picture of each child's hand preference and no demonstration is needed. Each child is classified objectively as right or left-handed. The importance of this documentation is related to the role of brain hemisphere in relation to the laterality of the truncal asymmetry and the curve, [39].

Similarly, the hair color, (dark, bright -for example blond) is recorded. AIS seem to have brighter hair color, [5].

The arms' span in cm is measured and written in the form. In heathy adolescents, body height and arm span are similar. However, in AIS, arm span can be used as a substitute for falsely low body height due to spine curvature to calculate other parameters, e.g. pulmonary, [40].

Several reports have found a different anthropometric profile among patients with AIS when compared with age and gender matched control subjects. In a study with a large sample size, girls with AIS were considerably taller, leaner, and had longer arm spans than their peers; arm span and sitting height independently predicted curve severity. It was suggested that this is the result of an aberrant growth pattern related to the cause of AIS and its curve progression, [41, 42, 43, 44, 45].

The following parameters are optionally measured and recorded, depending of the manpower and the objectives of the SSS team's project.

The head diameter (frontal and sagittal in cm) is measured. In infantile idiopathic scoliosis it is reported that there is face asymmetry. A comprehensive evaluation should be performed to identify commonly associated conditions, such as plagiocephaly, congenital heart disease, inguinal hernia, and hip dysplasia, [46, 59].

Trans-acromial distance in cm, trans-iliac distance in cm, trans-trochanteric distance in cm, thoracic diameter (frontal in cm and anteroposterior in cm), also humerus forearm, hand, femur, tibial, and foot right and left in cm may be measured. These parameters are needed for the study of the body structure and asymmetries seen in AIS patients, [45, 59].

Any lumbar ATI scoliometer's increased reading by conducting the Adam's standing test, raises the suspicion of a leg length inequality (LLI). In case of LLI, it is useful to assess which bone/s of the leg, or one of the hemi-pelvises, or combination of some or all of them, are longer or shorter and responsible for the LLI. This can be achieved either by using a measuring tape and assessing the superior anterior iliac spine to medial malleolus distance bilaterally or by asking the placed on an examination bed examinee to bent his knees and observe the possible asymmetry at the levels of the knees. This LLI initially results in functional spinal deformity, which later during growth, if the LLI persists, remodels to structural spinal scoliosis and can be easily prevented by shoe elevations at an earlier stage, [47, 48].

The right and left trans-malleolar distance in cm, [59], and the length of right and left Achilles (short or normal) tendon are assessed, [59]. Observing from behind the erect examinee, in case of Achilles tendon shortening in one site, the examiner ascertains that the resting calcaneal stance position angle is increased resulting in valgus hindfoot. This increase shortens the affected foot's leg length, even slightly, disturbing the horizontality of the pelvis, also contributing to the lumbar spine curvature, [49, 59].

D-d. Truncal examination

The examiner may observe the erect child from behind and see if the body tilts to one side, if there is asymmetry in the shoulders, asymmetry in the space between the trunk and the upper limbs, or a not horizontal pelvis.

The next mandatory assessment, during SSS program implementation, is the examination for any truncal asymmetry by conducting the Adam's bending test in standing and sitting position using always a scoliometer. Smart-phones loaded with the proper software may be used as scoliometers as well, with acceptable validity and accuracy, [50, 51].

Trunk asymmetry is recorded for mid-thoracic (T4–T8), thoracolumbar (T12–L1) and lumbar (L2–L5) regions. For the standing forward bending posi-

Table 1. The Protocol.

Protocol for the STUDY OF SCHOOL POPULATION

Region..... Date of examination ... / ... / 2022...

A. Personal Data

Surname.....Name.....Father's name .....Mather's name .....

Address: street..... number..... City..... Telephon:.....

School: **Primary** .....Grade ..... **High School** ..... grade

B. Basic Data

Birth place of the examinee..... Date of birth ....

Birth place of Father..... Father's profession ..... Father's age in years.....

Birth place of Mather..... Mather's profession ..... Mather's age in years .....

C. Biological and somatometric data

Sex: male , female. Menarche for females: month..... year....., Standing Height in cm..... Weight in Kg..... Gait in-toeing out-toeing neutral

Eyes' color: dark...., bright (green or blue)..., Sitting height cm..... Handedness: Right hand ....., Left hand.....

Hair color: dark...., bright (for example blond) arms' span in cm..... Head diameter: frontal in cm..... sagittal in cm.....

Trans-acromial distance in cm..... , trans-iliac distance in cm..... , trans-trochanteric distance in cm...., **Thoracic diameter**: frontal in cm....., anteroposterior cm.....

Bracket (humerus) length right in cm ....., left in cm....., forearm lenght right in cm....., left in cm....., Hand length: right in cm....., left in cm.....

Femur Length: right in cm....., left in cm....., Tibial Length: right in cm....., left in cm....., Foot Length: right in cm....., left in cm.....

Trans-malleolar distance: Right in cm....., Left in cm.....

Length of Achilles tendon: Right: short...., normal...

Left: short...., normal...

D. Scoliosis

Clinical **Radiological** **Hump (ATR) Scoliometer**: Right Thoracic in °....., Thoraco-Lumbar in °....., Lumbar in °.....

No scoliosis Left Thoracic in °....., Thoraco-Lumbar in °....., Lumbar in °.....

Yes Scoliosis degrees from to **Type of scoliosis** **Comments**

Thoracic Left (Thl) .... 1. Idiopathic .....

Thoracic Right (Thrt) .... 2. Congenital .....

Thoraco-Lumbar Left (T-Ll) .... 3. Paralytic .....

Thoraco-Lumbar Right (T-Lrt) .... 4. Neurofibromatosis .....

Lumbar Left (Ll) .... 5. Functional .....

Lumbar Right (Lrt) .... 6. Due to Leg Length inequality: .....

Kyphosis..... ....

Lor .... Are they aware that the child have scoliosis ? yes • no •

E. Clinical descriptions of the findings:

For example: developmental abnormalities, ect

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tion (StFBP) the examinee is asked to bend forward, looking down, keeping the feet 15 cm apart, knees braced back, shoulders loose and hands positioned in front of knees or shins with elbows straight and palms opposed. Any leg length inequality is not initially corrected. The side of the hump determines the laterality of trunk rotation. Trunk asymmetry (hump) to the right side is defined as right asymmetry and to the left is defined as left asymmetry in each of the three mentioned regions and recorded in degrees in the form, [39, 52]. For the sitting forward bending position, (SiFBP), the examinee is seated on a chair or stool (approximately 40 cm high) and is asked to bend forwards and place the head between the knees with the shoulders loose, elbows straight and hands positioned between knees. The scoliometer measurements are obtained successively at the same three areas of interest similarly to the standing forward bending position, [53].

After the Adam's StBFT, the Adam's SiBFT is carried out. Performing this test in sitting position, the pelvice becomes horizontal and the effect of any LLI on the truck is eliminated, therefore, any truncal changes in children with mild LLI are also reduced, [47].

This test is also useful in case of any truncal asymmetry at the lumbar level when performing the Adam's StBFT. Doing so, the real truncal/spinal asymmetry is revealed, because as it is reported, in healthy children, a physiological shortening of one leg (1–2 cm) is associated with a contralateral hump on the back in forward flexion not only at L3 but also at T12 and T8 vertebrae, [52].

The examined children with truncal asymmetry are referred to the scoliosis clinic of any legislated and specialized organization, (hospital, foundation, etc) for further evaluation. The SSS team, as it was noted before, has in advance prepared and printed a letter of invitation for re-assessment at the scoliotic clinic of the asymmetric children, which is handed to the headmaster of the school or the examined children to present to their families.

Growth has a significant effect in the correlation between the thoracic and the spinal deformity in girls with IS. Therefore, it should be taken into consideration when trying to assess the spinal deformity from surface measurements. It was reported that in IS during growth the rib cage deformity precedes the spinal deformity in the pathogenesis of idiopathic scoliosis, [15]. Therefore, our referral recommendation for re-examination at hospital is the following: if the child is less than 14 years of age and the scoliometer' s reading, (angle of trunk inclination / angle of trunk rotation (ATI / ATR)) is ≥ 6 degrees, as well as if the child is 14 or older than 14 years of age and the ATI/ATR is ≥ 5 degrees.

The referred children to the scoliosis clinic from the SSS programs are clinically and if indicated, radiographically examined. During the implementation of a SSS program, it is obvious that any other developmental abnormality is documented.

This described protocol has been used during the implementation of our SSS. The collected data were processed using the SPSS statically package. The outcome, except from the prevention and early management of IS, was the publications documenting numerous of the above parameters for the Hellenic school population, introducing the norms as well as a number of new concepts. Some of these studies are cited in this report and some other will be presented in a following article, where the results of our SSS program will be analyzed. The ultimate aim is not only the prevention and early management of IS, but its deeper study as well and a possible contribution to the knowledge of its aetiology, looking forward to an aetiological therapy of this condition in contrast to the symptomatic one, as it is today.

Abbreviations

ATI = angle of truncal inclination, ATR = angle of truncal rotation, AIS = Adolescent Idiopathic Scoliosis, BMI = body mass index, DRCS = double rib contour sign, IS = idiopathic scoliosis, IIS = Infantile Idiopathic Scoliosis, IVD = intervertebral discs, AIS = adolescent idiopathic scoliosis, LLI = Leg length inequality, LHS = leptin-hypothalamic-sympathetic, RI = Rib Index , RVA = Rib Vertebral Angle, RVAD = Rib Vertebral Angle Difference, StFBP test = forward bending position test, SiFBP = sitting forward bending position, SSS = School scoliosis screening , SE = standing erect, ST = surface topography, TA = trunk asymmetry, TR = thoracic ratio,

4DF = 4D Formetric

Competing interests

The author declares that he has no competing interests.

Author's contribution

The author was responsible for organizing the SSS program, its protocol and the examination team, managed the administration of it, involved in the examination of children, the collection of all data, conceived and postulated the described concepts written in this report, implemented the literature search and drafted this manuscript.

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School scoliosis screening, a program useful not only for the prevention of scoliosis. Part two: a clinical research tool for the study of the aetiology of idiopathic scoliosis.

Theodoros B. Grivas

ABSTRACT

This report presents the contribution of the school scoliosis screening program on aetiology/scoliogeny of idiopathic scoliosis. A number of issues are discussed related to the analysis of collected data from scoliosis school screening , namely the study of the influence of environmental factors in IS prevalence, that is the geographical latitude, menarche and the role of melatonin in IS pathogenesis, the relevance of scoliosis in women with visual deficiency, the age at menarche and its relation to laterality of the curve, the role of the brain in truncal asymmetry and idiopathic scoliosis pathogenesis, the thoracic cage in normality and its role in IS pathogenesis. We present the introduction of segmental thoracic ratios method and of the segmental Rib Vertebra Angles and Rib Vertebra Angle Differences in thoracic radiographs. The relative narrowing of the chest during growth: a hypothesis involving pelvic and thoracic inertia in gait and the introduction of double rib contour sign and the Rib Index. The impact of the lateral (sagittal plane) spinal profile, the role of the intervertebral discs in IS pathogenesis and the association of cavus foot with IS are also discussed. Additionally, the analysis of the somatometric parameters, the study of surface topography and the role of leg length inequality are presented. A pathophysiologic concept possibly common with IS is postulated studying the BMI in relation to the asymmetrical healthy adolescents. The parental age at birth is presented as a possible epigenetic factor/mechanism for the truncal asymmetry of a child. Finally, we summarize the outcomes and the hypothesized concepts related to IS scoliogeny, resulting from our SSS program, and our related publications on all the above discussed topics.

KEYWORDS: school scoliosis screening, aetiology, idiopathic scoliosis, environment, IS prevalence, geographical latitude, menarche, melatonin, IS pathogenesis, visual deficiency, age at menarche, curve laterality, brain, truncal asymmetry, thoracic cage, segmental thoracic ratios, segmental rib vertebra angles, segmental rib vertebra angle differences, growth, thoracic inertia, gait, double rib contour sign, rib index, lateral spinal profile, sagittal plane, intervertebral disc, cavus foot, somatometric parameters, surface topography, leg length inequality, BMI, epigenetics, parental age, IS concepts.

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"Mother nature created the spine articulated and mobile and we have to take any effort to keep it like this"

Introduction

The knowledge of normality is necessary for the study of abnormality. In this context the school scoliosis screening (SSS) programs serve the study both of these conditions, that is the study of normality and abnormality in children and adolescents during growth. Through the implementation of SSS programs data of growing school children and adolescents are collected and analyzed. Consequently, the axiom that the anatomy/morphology, may express/reflect and decipher/decode the physiology and pathology is used to clarify possible "paths" related to the understanding the scoliogeny.

At the beginning of our SSS program in 1997, we examined not only children of the ages according to the existing policies, that is approximately children from 9-14 years of age, when 85% of clinically significant IS appear [1,2], but we also screened pupils/students from 6 - 18 years old, namely from the first elementary grade [5-6 yrs. of age] to the last grade of high school [17-18yrs of age]). The beneficial result of this policy was that we had a great opportunity to collect data from a wide age range of the examined school children and adolescents.

The original main aim of the SSS programs is to identify most or all the individuals with unrecognized idiopathic scoliosis (IS) at an early stage when a less invasive treatment is more effective, in other words it is prevention. Beyond its original aim, SSS programs provide the opportunity for collection of various cross-sectional data, a) of normal children of general population [high, weight, menarche, handedness etc.] and b) similar data of asymmetric/scoliotic children and adolescents. These programs also enable the comparison of normals to asymmetric/scoliotics children and adolescents. Therefore, SSS programs are a "human evidence- based" "clinical research" tool of IS aetiology-scoliogeny based on the study of humans not animals, based on the above-mentioned axiom of the association of the anatomy/morphology to physiology/pathology.

The SSS offered information for the epidemiology and natural history of adolescent IS (AIS), [3,4]. Analysis of our domestic SSS programs, performed at the various cities of Greece, documented the national incidence of IS, and the estimation of the probable number of children who will need to be conservatively or surgically treated, [5,6].

During the years 1975 - 1999, 17 School Screening programs were performed in Greece and their results were analyzed and published in the book " School Screening in Greece", [2]. From the data of 1998 Hellenic National Census, the population of children aged 8 to 14 years old was approximately 751.000. With the above - mentioned datum and with a national mean IS incidence of 2.9%, (Cobb angle ≥ 10°), 21.779 children were expected to have scoliosis of variable severity. 980 of them would need conservative treatment using a brace, while 41 children would need surgical treatment, [5].

The examination of the role of the industrial environment on IS prevalence in the industrialized region revealed that prevalence was similar to this observed in other non-industrialized geographical departments of the country. This implies that industrial environmental factors probably do not significantly influence the prevalence of AIS, [7].

Further in this report the outcomes of our SSS program are summarized and the contribution of these studies on aetiology/scoliogeny of IS, Table 1.

1. Study of the influence of environmental factors in IS prevalence (geographical latitude), menarche and the role of melatonin in IS pathogenesis.

In the international peer review published literature, the IS prevalence is dissimilar in various geographic latitudes, namely higher values are reported in northern countries. The regression of prevalence of IS of each place by the latitude of the place where each study was conducted, was found statistically significant ($p < 0.001$). This observation could be related to the influence of the geography of a specific region on human biology and could be affected by socioeconomic and environmental factors such as temperature, humidity or light, [8, 9].

The above finding was documented using peer review reports of IS prevalence in countries only of the norther hemisphere. Currently we encourage

TABLE 1.

Contribution of the SSS program on aetiology/scoliogeny of idiopathic scoliosis (IS)

a. Study of the influence of environmental factors in IS prevalence (geographical latitude) and the role of melatonin in IS pathogenesis
b. prevalence of scoliosis in women with visual deficiency
c. age at menarche in IS girls and its relation to laterality of the curve
d. the role of the brain in trunk asymmetry (TA) and IS pathogenesis
e. thoracic cage in normality and its role in IS pathogenesis/scoliogeny
f. the impact of the lateral spinal profile (LSP), (sagittal plane)
g. the role of the intervertebral discs (IVD) in IS pathogenesis
h. association of cavus foot with IS
i. anthropometric data in IS patients
j. SSS referrals and surface topography (ST)
k. SSS referrals and Leg Length Inequality (LLI)
l. Study of the BMI in relation to the TA of healthy adolescents, a pathophysiologic concept possibly common with IS
m. Parental age at birth as a possible epigenetic factor/mechanism for the TA of child

similar studies in the southern hemisphere counties in order to confirm the results. The initial findings show that countries further southern from the equator like Chile, have increased value of IS prevalence, [10]. Similar studies are now organized and being contacted in Brazil and Indonesia, countries that extend from the equator and much further south.

In peer review published literature the menarche is reported to be different in places of various geographic latitudes, namely in higher values in northern countries. Consequently, we hypothesized a possible association between prevalence of IS and age at menarche among normal girls in various geographic latitudes, [11].

The regression of prevalence of IS and age at menarche by latitude documented for each study, was found statistically significant ($p < 0.001$) and both were following a parallel ascending course of their regression curves, especially in latitudes northern than 25 degrees. This means that late age at menarche is matching with higher prevalence of IS, a finding which was not reported earlier in the available to us peer review literature.

Melatonin, "the light of night", is secreted from the pineal gland, principally at night. Among other biological functions, the hormone is involved in the sexual maturation of females, [12]. Melatonin acts in gonads indirectly, reducing the secretion of gonadotropins and mainly the luteinizing hormone (LH), [13]. The menarche is related with episodic secretion of LH during the night, [14, 15]. Melatonin may play a role in the timing of puberty and the onset of puberty in humans may be related to the decline in melatonin secretion that occurs as children grow, [16]. We hypothesized that the amount of light, which is different in different geographical latitudes influences melatonin secretion and alters age at menarche. Delayed puberty results in a prolonged period of spine vulnerability when other aetiological factors are contributing to the development of IS, [11]. Furthermore, we found that this positive association between prevalence of IS and geographic latitude is present only in girls and not in boys. This contradictory association implicates that the possible role of environmental factors acts in a different way between boys and girls, [8].

The role of melatonin deficiency in IS pathogenesis was proposed after development of scoliosis similar to those of human's IS in pinealectomized chickens, [17]. Fagan et al, 2009, reported that caution is advised when drawing conclusions regarding the pathogenesis of AIS from this model, [18]. Several other publications argued that there is a controversy whether chickens are appropriate models for studying scoliosis, because they present extrapineal sites of melatonin production that contribute to circulating melatonin levels, in contrast to humans that no extrapineal sources affect the circadian rhythm of melatonin. Melatonin's actions appear to differ between humans, other mammals, and other vertebrates, [19, 20, 21, 22, 23]. Also, pinealectomy in bipedal nonhuman primates did not produce scoliosis in any of the 18 monkeys examined in a mean follow up period of 28 months, [24]. Furthermore, no increased IS prevalence has been observed in children after pinealectomy or pineal irradiation because of pineal neoplasias, although they have a lack of serum melatonin in the majority of studies, [25, 26, 27].

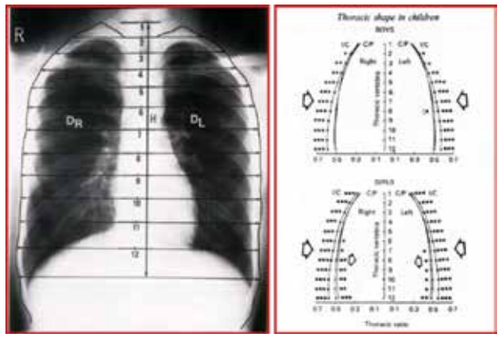

Figure 1. *Left figure - Chest radiograph to show the method of measurement for calculation of thoracic ratios (TR) fromT1-T12. DR (DL) = distance measured from midpoint of the distal end-plate of each vertebral body (Tl- 12) to the outline of the lateral border of the right (left) thoracic cage. H = distance from Tl- 12. Right figure - TRs for infancy (I), childhood (C) and puberty (P). (Modified from Grivas et al 1991). [38].*

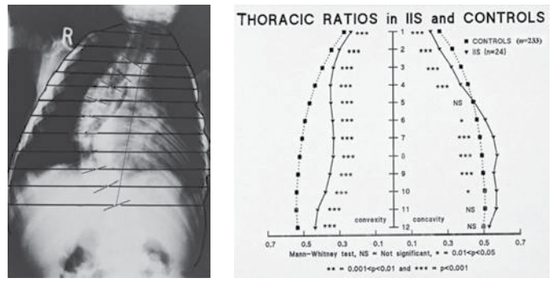

Figure 2. *In IIS the thoracic cage is under-developed compared to non-scoliotic counterparts. (Modified from Grivas et al 2006), [34].*

2. Prevalence of scoliosis in women with visual deficiency.

Girls with visual deficiency were found to have a delayed age at menarche (13 years old versus 12.58 years of controls) and their prevalence of IS was found to be much increased (42.3%). This is strongly supporting the hypothesis that in blind girls, the lack of light through the increased levels of melatonin may delay sexual maturation and expose for longer period the growing immature spine to detrimental causative factors of IS, which result in increased IS prevalence, [28].

3. Age at menarche and its relation to laterality of the curve.

The age at menarche in IS girls is reported to be delayed, compared to nonscoliotic girls. This generalized statement questions the accuracy of reported records for age at menarche which are found different at different geographical latitudes. Our findings, derived from our SSS program referrals in Greece, didn't show any statistically significant difference of the age at menarche between scoliotic and non-scoliotic girls, [29]. Additionally, analyzing the laterality of the curve in relation to age at menarche we found that premenarchal IS girls presented predominantly with a left primary scoliotic curve, while postmenarchal IS girls presented predominately with a right primary scoliotic curve [30]. This observation which associates the age of IS onset with the laterality of the curve requires further investigation and this finding would not be figured out without running a SSS program, [30]. Both of the above-described findings (no different menarchial onset of the non-IS and IS girls and the different laterality of the curves in pre and post menarchial IS girls) were confirmed in a recent research study in Serbia and Bosnia – Herzegovina, areas with almost similar geographical latitude with Greece, [31]. As known, in infancy when boys develop IS, they are more frequently presented with left sided thoracic curves. Our finding on laterality of curves in pre-menarchial scoliotic females, revealed by the analysis of data of the referred children from SSS, justifies the hypothesis that the pre-menarchial developed left curves may be due to the same mechanisms/causes with those functioning for the more frequently developed left thoracic curves in infant IS males. This finding may be due to the impaired development of

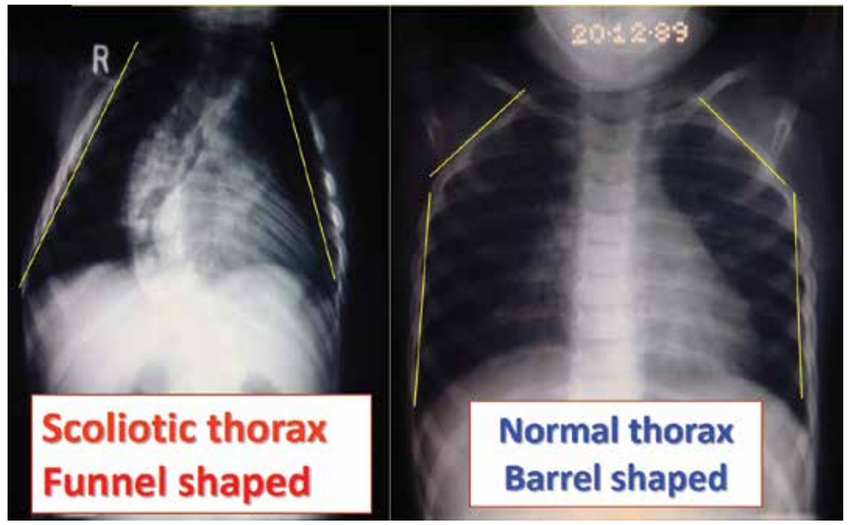

Figure 3. *The thorax in IIS is funnel shaped compared to the thorax in controls which is barrel shaped.*

the infantile scoliotic thoracic cage, but this suggestion needs more investigation, [32, 33, 34, 35].

4. The role of the brain in TA and IS pathogenesis.

The analysis of the data for truncal symmetry and asymmetry using the scoliometer, collected from our SSS program, from symmetric controls and asymmetric children showed that there is a significant correlation of mild mid-thoracic asymmetry to the dominant brain hemisphere in terms of handedness, in children who are entitled at risk of developing IS, [36, 37].

5. The thoracic cage in normality and its role in IS pathogenesis/scoliogeny

The introduction of segmental thoracic ratios (TR) method in thoracic anteroposterior radiographs. This new segmental thoracic ratios (TR) radiographical method of segmentally assessment of growing normal thorax from T1-12, was conceived and presented by the author, [38]. On each chest radiograph, the outline of the lateral border of the thorax is drawn, (Figure 1). Next, the midpoint of the distal end-plate at each vertebral body from Tl- 12 is marked. Then, at each segment, the distance from the middle of the end-plate to the outline of each of the right and left thoracic cage is measured. These distances are standardized by dividing by the measured T1- T12 distance. They are termed segmental right and left thoracic ratios (TRs). Ratios are also calculated segmentally for the total width of the chest (right plus left measured lengths).

The TR method was used to study the thorax of infantile IS (IIS), and compare it with this of controls, figures 2. Using the segmental TRs method it was shown that in IIS the thoracic cage is under-developed compared to non-scoliotic counterparts. The thorax in IIS is narrower than that of the controls, the upper chest is funnel-shaped, figure 3, and there is a predictive value of the vertebral rotation* at the upper limit of the thoracic curve of IIS, that is the vertebral counter-rotation at T4 predicts the apical vertebral rotation at follow-up, which reflects impaired rib control of spinal rotation possibly due to neuromuscular factors, which contribute also to the funnel-shaped chest, (*compared with specific rotation of Perdriolle and Vidal - the so called "specific angle of rotation". In an anteroposterior roentgenogram, specific rotation (RS) is the sum of the rotation in the axial plane of the two vertebrae adjacent to the superior end vertebrae). [32, 39, 40, 41].

The introduction of the segmental of Rib Vertebra Angles (RVAs) and Rib Vertebra Angle Differences (RVADs) in thoracic anteroposterior radiographs, (figures 4,5,6).

The apical RVA and RVAD was initially (1972), presented by Mehta, [42]. This radiographical method of segmental RVAs and RVADs from T1-12, was for the first time presented for the study of the growing normal thorax, [37], (Figure 4, 5, 6).

The RVAs are a functional index which is visible on the chest radiographs. It was suggested that the differences of the RVAs between right and left side is the expression of asymmetric muscle forces acting on the thoracic cage, which deforms early and possibly transfers the deforming forces to the spine. It is concluded that that measurement of the RVAs, whether as apical RVAD or as segmental RVAs gives early information about the process of curve initiation and progression. Significantly asymmetric RVAs have been observed even at Cobb angles of 8°, i.e. before the diagnosis of scoliosis is made, [43].

Segmental Rib vertebra angle difference (asymmetry) (RVAD) in controls.

Left RVA minus Right RVS mean in degrees

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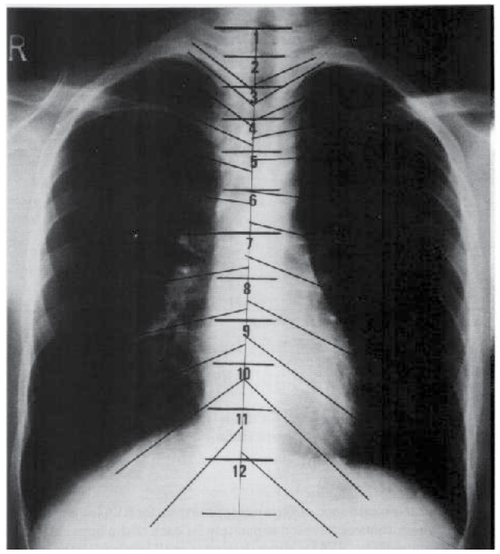

Figure 4. *Segmental rib-vertebra angles from T1-T12, (modified from Grivas et al 1992).*

Comparing the RVAs between the mild late onset IS (10—20 Cobb degrees) and nonscoliotic children, it is shown that the late onset IS children rib cage had lower RVAs, that is the thorax is narrower. This indicates that the scoliotic thorax is under-developed compared to non-scoliotic counterparts, [44], Figure 7.

During growth the thorax remodels. The drooping of the lower ribs of girls, which is more evident than in boys, occurs between infancy and childhood, or largely before the girl's pelvis increases in size, [37, 38, 44, 45, 46, 47a, 47b, 48].

Relative narrowing of the chest during growth: a hypothesis involving pelvic and thoracic inertia in gait.

We postulated a hypothesis, namely that the mechanism by which this rib droop occurs is through neuromuscular factors. Between childhood and puberty, the increased rotational inertia generated by the larger pelvis of girls is not associated with further lower rib drooping but, we suggest, with rib growth impairment (relative to spinal growth) in the lower half of the chest. During the same developmental period (childhood to puberty), boys show no further relative narrowing of the chest, [49, 50].

Also, our hypothesis is that the relative diminution of TRs particularly of the lower thorax with increasing age in boys and girls may be a mechanism to reduce the rotational inertia created in the thorax from the rotating thoracolumbar spine and pelvis in gait, [51, 52]. Such a mechanism would conserve energy. It will be recalled that inertia (I) equals Σmr^2, (where Σ =sum, m= mass and r = radius). Hence, a relative diminution of thoracic width would produce a much greater reduction of rotational inertia, because inertia is a function of the square of the distance. In evolutionary terms, the chest narrowing is consistent with an adaptation of the human ribcage to bipedal gait. This hypothesis suggests that RVA drooping, as a mechanism to narrow the chest for mechanical reasons (energy conservation), can go so far; below a certain RVA droop, rotation control of the spine would be compromised. To avoid this situation in girls, rib growth is impaired in order to narrow the lower thorax further between childhood

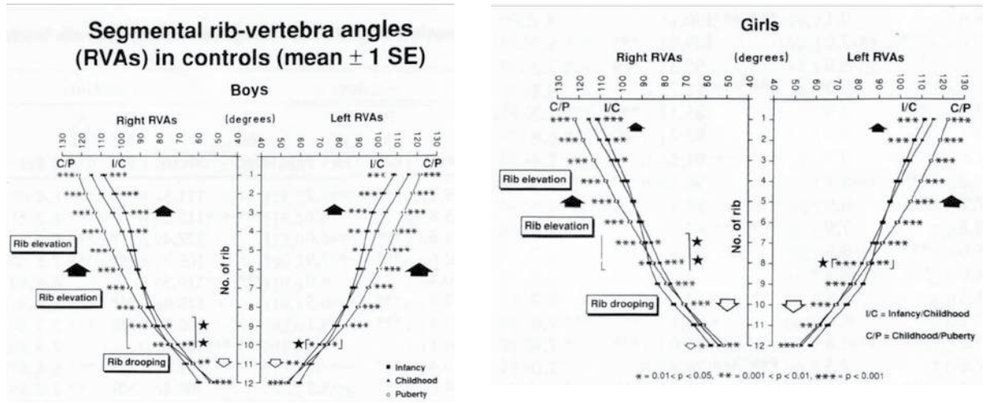

Figure 5. *Segmental rib-vertebra angles (RVA's in degrees) in boys and girls for each of the infancy (I), childhood (C), and puberty (P) groups by rib level. (modified from Grivas et al 1992).*

and puberty to lessen the rotational inertial burden, [37].

The introduction of double rib contour sign (DRCS) and the Rib Index (RI) (Fig. 8).

This sign and index were initially presented in Greece during the 25th "Nicolas Giannestras-Panayiotis Smyrnis" Anniversary Symposium of Spinal Column Diseases, at the Porto Rio Hotel, Patras, Greece, 21-23 May 1999, [53]. Later it was presented in the International Research Society of Spinal Deformities meeting at Clermont Ferrand, Château du Marand, France, 23-26 May 2000, [54], and it was published in 2002. This publication focused on the implications of DRCS on the aetiology of idiopathic scoliosis, [55].

All lateral spinal radiographs in IS show a DRCS of the thoracic cage, a radiographic expression of the rib hump (RH), Figure 8. The outline of the one hemi-thorax (convex) overlies the contour of the other hemi-thorax (concave). Then the rib index (RI) method extracted from the DRCS was introduced in order to quantify the severity of the double rib contour (DRC) that is to evaluate the rib hump deformity, in IS patients in an attempt to create a safe reproducible way to assess the RH deformity based on lateral radiographs. This assessment actually represents the appraisal of the transverse plane rib-cage deformity, a method applied to the lateral spinal radiographs. The application of Rib index is useful for documentation of the thoracic deformity before any treatment, the assessment of physiotherapy treatment, the assessment of brace treatment and the pre- and post-operative assessment of the rib-cage deformity correction on the transverse plane, [56].

The effect of growth on the correlation between the spinal and rib cage deformity.

Growth has a significant effect in the correlation between the thoracic and the spinal deformity in girls with idiopathic scoliosis. Using the RI as an expression of the thoracic deformity and Cobb angle as an expression of the spinal deformity, the existence of any correlation between these two parameters was tested. Linear association was seen only between thoracic Cobb angle and rib-index in the age group of 14–18 years. (Predicted Thoracic Cobb Angle = - 6.357 + 7.974 × (Rib-Index). Figure 9. This new finding was very interesting as it implicated that in younger children the thoracic deformity and the spinal deformity are not associated but only in older children, [57]. Dr Smyrnis 2000, seven years ago, observed this phenomenon based on his clinical experience only and noted it in his lecture published in the cited book, [2], that is "the most critical

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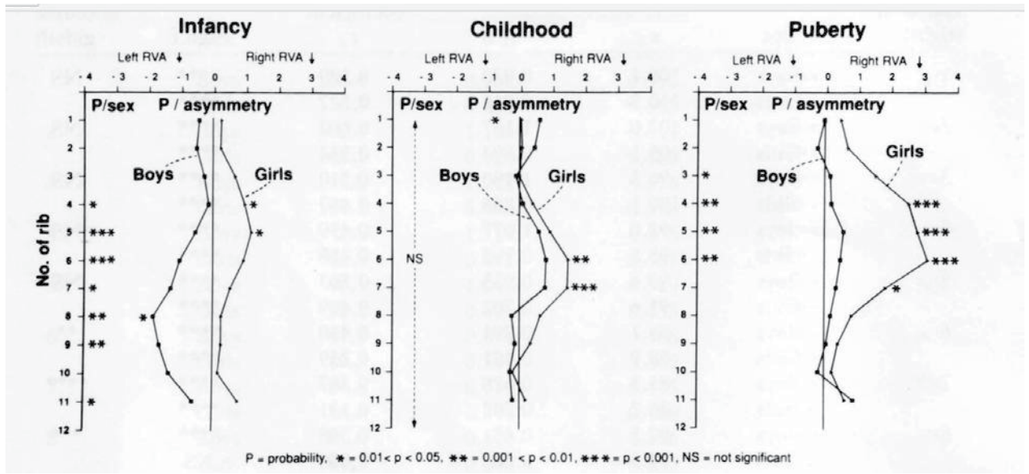

Figure 6. *Segmental rib-vertebra angle asymmetry (rib-vertebra angle difference, RVAD) in the "normal" boys and girls for each of the infancy (I), childhood (C), and puberty (P) groups. Overall, the pattern of this " normal" RVA asymmetry reflects the age, sex, and laterality patterns of IS. It suggests that extremes of RVADs may be etiological factors for both infantile and AIS. (Modified from Grivas et al 1992).*

age for mass screening is from 10-13 years old, and in this cohort of ages it is usually observed 3:1 ratio between clinically and radiologically positive children".

Growth seems to have a significant effect in the correlation between the rib cage and the spinal deformity in girls with IS. The findings of this study support the hypothesis that the correlation between thoracic surface and spinal deformity is weak in younger children, implicating that the thoracic cage deformity precedes that of the spine in the pathogenesis of IS, [57, 58].

6. The impact of the lateral (sagittal plane) spinal profile (LSP).

In a study of children, referred from our SSS program, suffering mild (10-20 degrees) IS, it was found that the LSP in thoracic spine hypokyphosis is not a predisposing aetiological factor. This was concluded because in the initiation of IS curves the LSP is similar to that of their healthy controls, [59]. This study provides evidence that thoracic hypokyphosis by alleviating axial rotation is rather a compensatory mechanism than an aetiological factor of IS pathogenesis, figure 10.

The above finding was confirmed in a recent study of the LSP of the spine in IS using the surface topography, scoliometric assessment and the radiographical imaging, [60]. Thus, it is clear that hypokyphosis is not a primary causal factor for the commencing of mild or moderate IS curve, but it could be considered as a permissive factor in the scoliogeny, [60], figure 11.

7. The role of the intervertebral discs (IVD) in IS pathogenesis.

In the postero-anterior radiographs of mild IS children referred from our SSS program, it was shown that the deformity appears first at the level of the IVD, which is found wedged. The deformity of the vertebral body in spinal column follows. The deformation of the apical IVD and its adjacent IVDs seems to be an important progressive factor in IS pathogenesis, [61, 62], figure 12.

8. Association of cavus foot with IS.

It is well known, that in a number of certain neuromuscular diseases cavus foot and scoliosis are

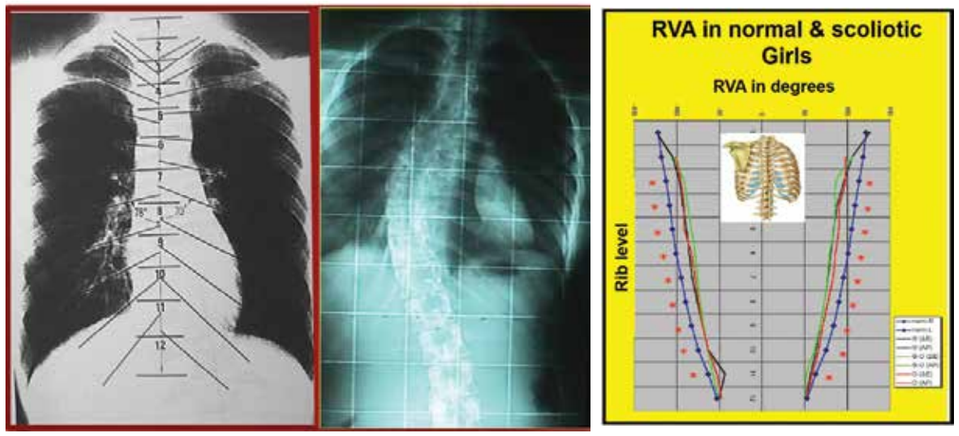

Figure 7. *The scoliotic thorax is under-developed compared to non-scoliotic counterparts. (Modified from Grivas et al 2002), [44].*

presented together. Such diseases are muscular dystrophy, cerebral palsy, Friedrich's ataxia, Charcot-Marie-Tooth disease, poliomyelitis, syringomyelia or spinal cord tumors. Having in mind this observation many authors studied the relationship between foot morphology (especially pes cavus) and scoliosis, as it was supposed that these pathologic conditions may share a common cause.

During the first 13 years (1996 – 2009) of our Thriasio Hospital SSS program implementation we also contacted foot printing. The Harris–Beath mat for foot-printing was used. We investigated if there is a relationship between cavus foot, type 1 of footprint [84], figure 13, and IS in a population referred from our SSS program. The significant correlation between IS and cavus foot as it has elsewhere been reported was not verified in our study. No positive correlation was found between IS and flat foot [84], type 6 of footprint, figure 13, as well in our study, [63, 83].

9. The somatometric parameters.

Analysis of our SSS program collected data yielded the somatometric parameters and comparison of these parameters of nonscoliotic children with their counterparts suffering mild IS. The scoliometer readings in both standing forward bending position (StFBP) Adam's test and sitting forward bending position, (SiFBP) test of 2071 children and adolescents (1099 boys and 972 girls) aged from 5 to 18 years old were studied. The mean frequency of TA of 7 or more degrees was 3.23% for boys and 3.92% for girls at the StFBP and 1.62% and 2.21% at the SiFBP, respectively. Girls are found to express higher frequency of TA than boys. Right TA was more common than left. The sitting position is the preferred screening position for examining the rib or loin hump during school screening as it demonstrates the best correlation with the spinal deformity exposing the real TA, [64]. The cross-sectional study of TA using the scoliometer, in normal juveniles provides data which describe the evolution of TA, from early childhood to adolescence. Juveniles were found more symmetric than adolescents, who were studied previously in a different study. Furthermore, juvenile girls were found more symmetric than boys. Juvenile TA pattern seems to be in accordance with the higher incidence of juvenile IS in boys. Furthermore, severe TA, which could be correlated with a scoliotic curve, was found to be more common to the left side. These reports provided information about the variability of back morphology in normal juveniles. The amount of TA detected in children during SSS, which may reveal a spinal curve, is the main indicator/marker for referral and further orthopaedic assessment but

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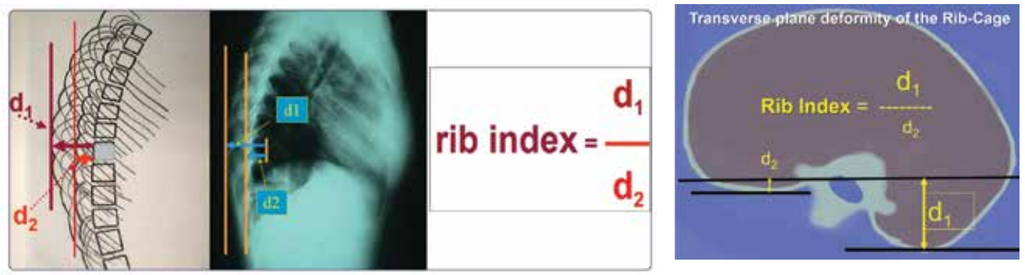

Figure 8. *The DRCS and the RI in the lateral thoracic radiographs used for the thoracic transverse plane deformity assessment, (Modified from [56]).*

can also be used as a baseline for further research on IS aetiology, [65, 66].

The creation of a database of the collected data with somatometric parameters, i.e. of body weight and height from the entire cohort of the SSS program children provided the opportunity to compare these parameters of nonscoliotic children with their counterparts suffering IS with curves of a Cobb angle 10 degrees. In our studied Mediterranean sample of the population, the somatometric parameters of height and weight in children with mild IS, regardless of curve type and site, were not found statistically different from their nonscoliotic counterparts, [67].

10. SSS referrals and surface topography (ST). (Figure 14).

The evaluation of the effects of the Adam's standing forward bending position (StFBP) test versus the standing erect (SE) position on back TA was conducted using the scoliometer readings in the Adam's StFBP and the 4D Formetric (the Diers surface tomography apparatus 4DF; Diers International, Schlangenbad, Germany) readings in the SE position. It was shown that back TA in children and adolescents differs in the StFBP and 4DF Erect (SE) positions. This is probably attributed to the complicated truncal anatomy, and the results of this study may be used as a useful foundation for further understanding of torso dynamics, [68].

11. SSS referrals and LLI.

In children and adults LLI may affect their posture, gait, and several truncal parameters, and it can cause scoliosis. In our study we assessed truncal and spinal changes due to mild LLI using ST analysis. The LLI was statistically significant correlated to the 4DF, reading of pelvis rotation, pelvic tilt (pelvic obliquity), and surface rotation. The scoliometer readings of ATR/ATI in the lumbar region were statistically significant correlated to the 4DF readings of pelvic tilt (pelvic obliquity). The normally symmetric truncal parameters were also statistically significant changed, all these deviating from the line of gravity through the vertebral prominence. Interestingly, LLI was not statistically significant correlated to the scoliosis angle and the scoliometer reading at the lumbar level, [69].

12. Study of the BMI in relation to the TA of healthy adolescents, a pathophysiologic concept possibly common with IS.

Studying the somatometric data collected from children examined in our SSS program, their body mass index (BMI) was calculated, that is the measure of body fat based on height and weight) and consequently we formulated the following hypothesis. This hypothesis suggested that the pathogenesis of severe TA in girls and boys, has the same mechanism as that proposed for AIS girls, namely: severe TAs are initiated by a genetically-determined selectively increased hypothalamic sensitivity (up-regulation, i.e. increased sensitivity) to leptin, with asymmetry as an adverse response to stress (hormesis), mediated bilaterally mainly to the growing trunk via the sympathetic nervous system (leptin-hypothalamic-sympathetic nervous system

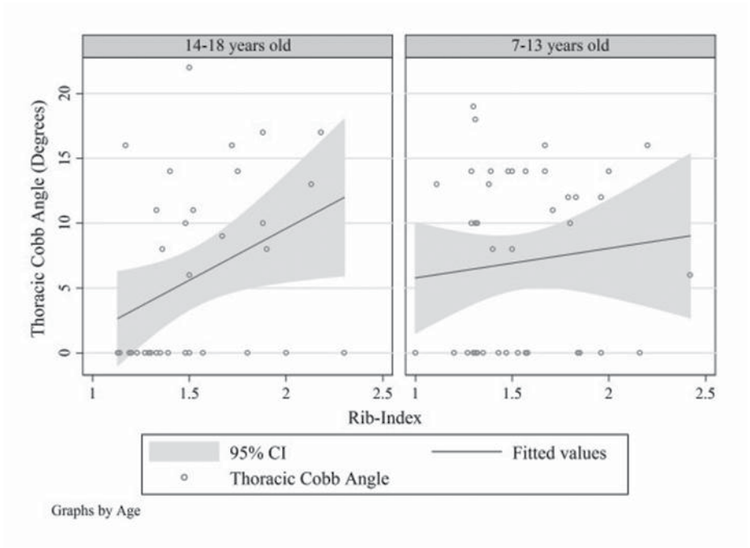

Figure 9. *A linear association was the one between Thoracic Cobb Angle and rib-index in the age group of 14–18 years not in younger aged girls. This implicated that in younger children the thoracic deformity and the spinal deformity are not associated but only in older children. (Predicted Thoracic Cobb Angle = -6.357 + 7.974*(Rib-Index). [57].*

(LHS) concept), [70].

13. Parental age at birth as a possible epigenetic factor/mechanism for the TA of child.

Parental age at birth is implicated as a possible epigenetic mechanism for the in TA of a child [71, 72, 73, 74]. The age of the mother as an environmental factor in the general population may potentially influence epigenetically the onset of TA in boys more than girls as well as during growth. The significance of the findings is based on the principle that the endometrial environment is vital to the planning of the fetus for health and illness throughout its life, [75, 76, 77]. Consistent findings reported from the USA, Edinburgh and Sweden reveal increased maternal age as a risk factor for AIS, suggesting maternal factors can predispose to it, [78 ,79, 80]. It seems that males are more affected by this factor but, unexpectedly in our study, by younger and not older mothers as reported for AIS in the literature, [81, 82].

It is very interesting to note that this clinical research on IS aetiology based on SSS is the only "Human evidence based" research contributing to our understanding of IS scoliogeny and we solidly recommend it.

In conclusion, the outcomes and the hypothesized concepts related to IS scoliogeny, resulted from our SSS program and the study of the imaging of non-IS and IS growing thoracic cages are outlines.

1. The amount of light, which is different in different geographical latitudes influences melatonin secretion and alters age at menarche. Delayed puberty results in a prolonged period of spine vulnerability when other aetiological factors are contributing to the development of IS, the prevalence of which varies in different geographical latitudes.
2. In norther geographical latitude the IS prevalence is higher.
3. The prevalence of IS is higher in females with Visual Deficiency.
4. Premenarchal IS girls present predominantly left primary scoliotic curve, while post-menarche IS girls present predominately right primary scoliotic curve
5. There is a significant correlation of mild mid-thoracic asymmetry to the dominant brain hemisphere in terms of handedness, in children who are at risk of developing IS.
6. Introduction of the segmental thoracic ratios method assessment of thorax in thoracic anteroposterior radiographs.
7. Introduction of the segmental of RVA and the segmental RVAD method for assessment of the growing thorax in thoracic anteroposterior radiographs.
8. The pattern of "normal" segmental RVAD in "normal" boys and girls for each of the infancy, childhood, and puberty groups, reflects the age, sex, and laterality patterns of IS. It suggests that extremes of RVADs may be etiological factors for both infantile and AIS.
9. The thorax in IIS is funnel shaped compared to the thorax in controls which is barrel shaped.
10. During normal growth the thorax remodels. There is drooping of the lower ribs both in boys and girls. The drooping of the lower ribs of girls, is more evident than in boys.
11. The relative narrowing of the lower chest during growth: a hypothesis involving pelvic and thoracic inertia in gait. The relative diminution of TRs and RVA particularly of the lower thorax with increasing age in boys and girls may be a mechanism to reduce the rotational inertia created in the thorax from the rotating thoracolumbar spine and pelvis in gait.
12. The introduction of DRCS and the RI. RI is used for a. the documentation of the thoracic deformity, b. assessment of physiotherapy, c. assessment of brace treatment and d. pre- and post-operative assessment; of the rib-cage deformity correction on the transverse plane.
13. The effect of growth on the correlation between the spinal and rib cage deformity. In younger children the thoracic deformity and the spinal deformity are not associated but only in older children.
14. The impact of the LSP, (sagittal plane). The LSP, (hypokyphosis) is not a primary causal factor for the commencing of mild or moderate IS curve, but it is a permissive factor for the scoliogeny.

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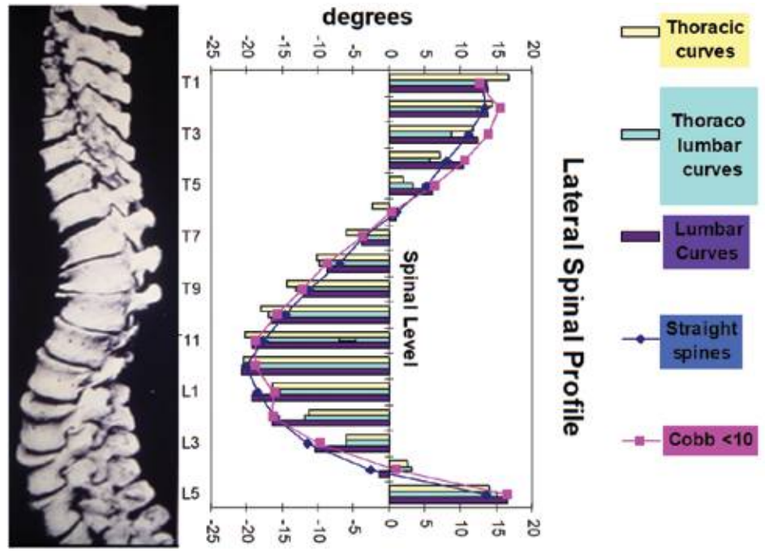

Figure 10. *The LSP in children with 1) straight spines, 2) with spinal curvature having a Cobb angle less than 10°, and 3) in scoliotic children with a) thoracic, b) thoracolumbar and c) lumbar curves. Comparing the children's LSP between the above groups, using Mann-Whitney test, it was shown that no statistical difference was noticed, in almost all spinal levels. (Modified by Grivas et al 2002, [59]).*

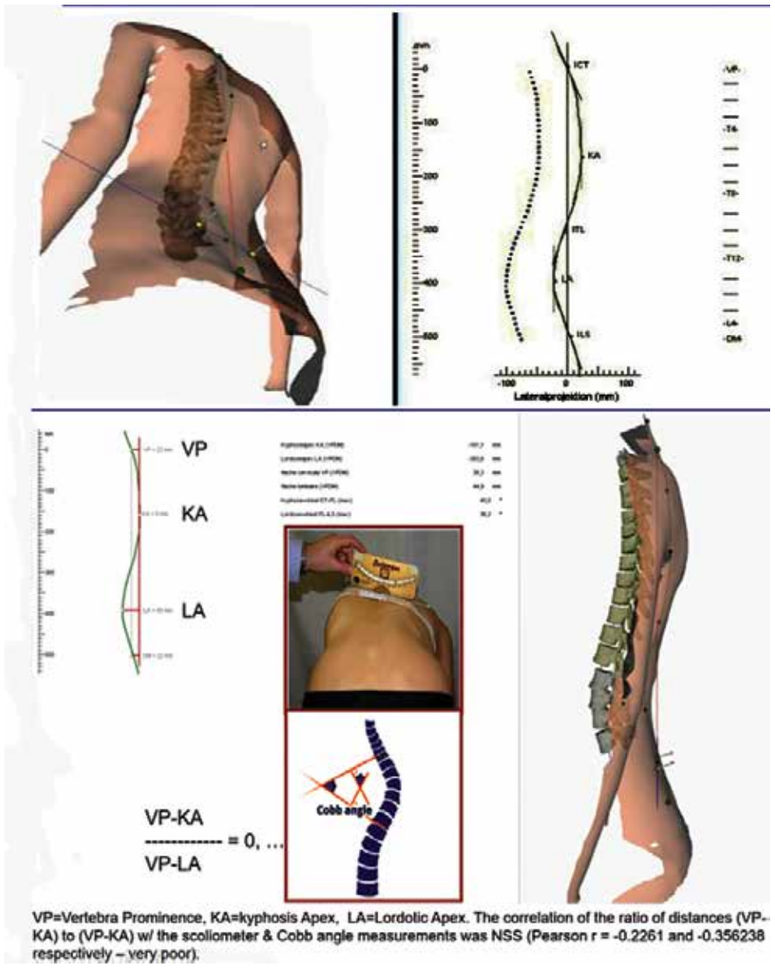

Figure 11. *Study of the sagittal profile of the spine in IS using surface topography. (Modified by Grivas et al 2021, [60]).*

15. The role of the intervertebral discs (IVD) in IS pathogenesis. The deformity appears first at the level of the IVD. The deformity of the vertebral body in spinal column follows.

16. There is no association of cavus foot and IS.

17. The somatometric parameters. Girls are found to express higher frequency of TA than boys. Right TA is more common than left. The sitting position is the preferred screening position for examining the rib or loin hump during SSS as it demonstrates the best correlation with the spinal deformity exposing the real TA.

18. SSS and ST. TA in children and adolescents differs in the StFBP and 4DF Erect (SE) positions. This is probably attributed to the complicated truncal anatomy, and the results of this study may be used as a useful foundation for further understanding of torso dynamics.

19. LLI and ST. LLI is not statistically significant correlated to the scoliosis angle and the scoli-

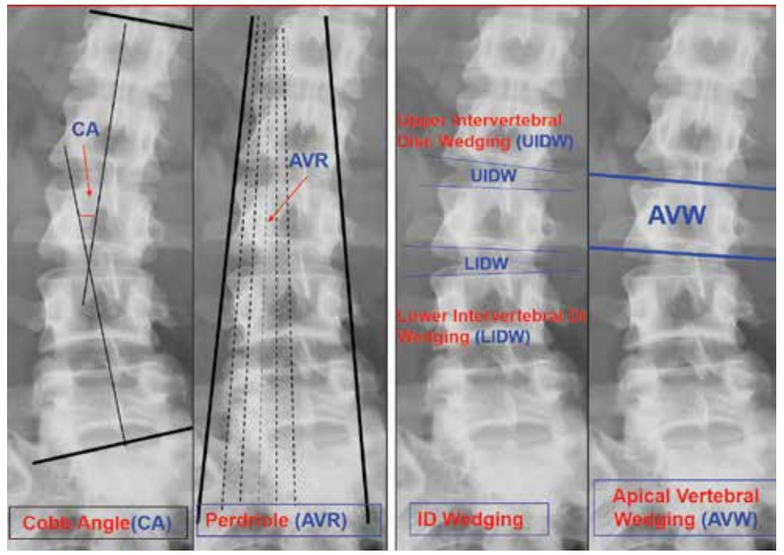

Figure 12. *The deformity appears first at the level of the IVD. (Modified by Grivas et al 2021, [61, 62]).*

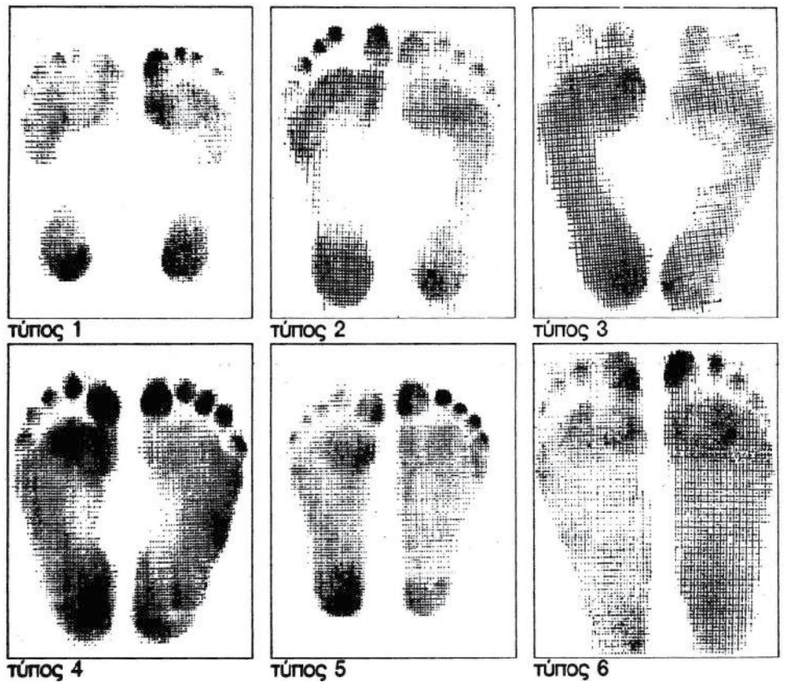

Figure 13. *The footprint type 1, of cavus foot, according to the 6 types of footprints, (Grivas 1984 [83]), was not associated with IS.*

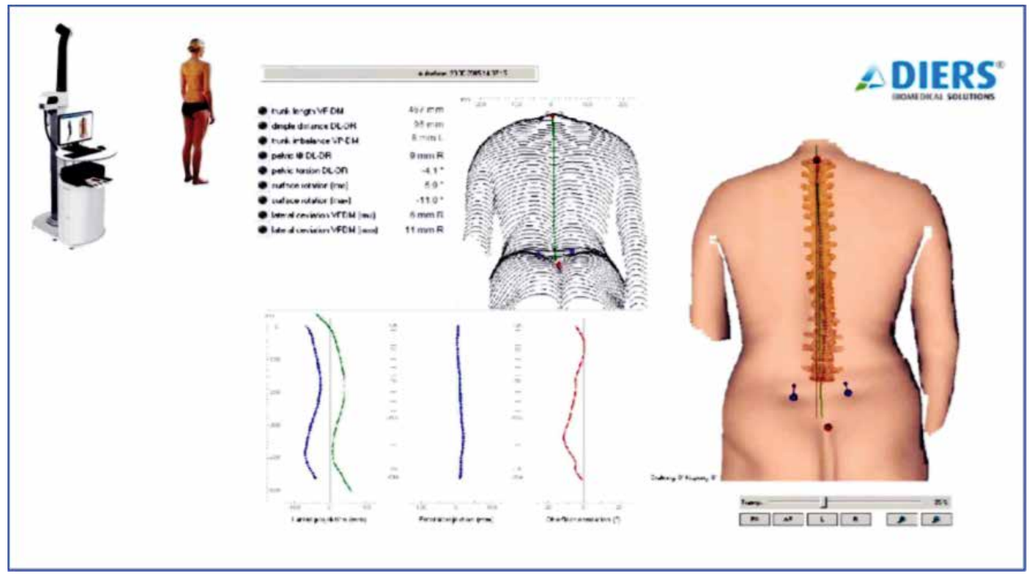

Figure 14. *Study of the LLI in children suffering mild IS using the 4DF apparatus. (Modified from [68]).*

ometer reading at the lumbar level TA in children and adolescents.

20. We postulated a hypothesis studying of the BMI in relation to the TA of healthy adolescents: we suggested a pathophysiologic concept possibly common with IS.

21. The parental age at birth is an epigenetic factor/mechanism for the TA of child. Males are more affected by this factor, if born by younger and not older mothers.

Abbreviations

ATI = angle of truncal inclination
ATR = angle of truncal rotation
AIS = Adolescent Idiopathic Scoliosis
BMI = body mass index
DRCS = double rib contour sign
IS = idiopathic scoliosis
IIS = Infantile Idiopathic Scoliosis
IVD = intervertebral discs
AIS = adolescent idiopathic scoliosis
LLI = Leg length inequality
LHS = leptin-hypothalamic-sympathetic
RI = Rib Index
RVA = Rib Vertebral Angle
RVAD = Rib Vertebral Angle Difference
StFBP test = forward bending position test
SiFBP = sitting forward bending position,
SSS = School scoliosis screening
SE = standing erect
ST = surface topography
TA = trunk asymmetry
TR = thoracic ratio
4DF = 4D Formetric

Competing interests

The author declares that he has no competing interests.

Author's contribution

The author was responsible for organizing the SSS program and the examination team, managed the administration of it, involved in the examination of children, conceived and postulated the described concepts written in this report, implemented the literature search and drafted this manuscript.

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Epidural hematoma following the use of an epidural catheter for continuous postoperative analgesia: A case report and review of the literature.

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ABSTRACT

Spinal epidural hematoma is a rare but a serious condition, with high morbidity and mortality, leading to significant neurological deficiencies. One of the main causes of spinal epidural hematoma is spinal puncture during anaesthetic procedures. We report an interesting case of an epidural hematoma following the use of an epidural catheter of continuous postoperative epidural analgesia (CPEA), following a Whipple procedure. This case is particularly interesting, due to the delayed onset of the hematoma, the total absence of predisposal factors and the uneventful patient's recovery following immediate surgical intervention.

KEYWORDS: Epidural anaesthesia, Epidural Haematoma

Introduction

The epidural space is the area defined centrally by the spinal sac and distally by the spinal canal; its anterior wall is considered to be the bodies of the vertebrae, whereas the posterior walls are the vertebral arches along with ligamentum flavum. Traditionally, the epidural space has been described as a consistent compartment surrounding the spinal sac. However, recent anatomical studies report that epidural space with its contents forms circular discontinuous compartments separated by zones where the dura mater comes into direct contact with the walls of the spinal canal [3,4].

A spinal epidural hematoma is characterized by the rarity of its occurrence but also its severity, as it is considered as an emergency medical condition [5]. To a great extent, its clinical presentation is characterized by pain at the site of the injury radiating distally to the extremities, progressing in most of the cases to various degrees of neurologic deficits. The first report in the literature was published by Jackson in 1869, describing the case as "spinal apoplexy" [6]. In 2017, Domenicucci et al. published an extensive review of the literature trying to gather all the reported cases of spinal epidural hematomas published between the years 1869 and 2012 [7]. As it is evident from the above extensive literature review, one of the main causes

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Fig. 1. *MRI T2 Sagittal*

Fig. 2. *MRI T2 Coronary*

of spinal epidural hematoma is spinal puncture during anaesthetic procedures [8,9].

The incidence of serious complications after the induction of neuraxial anaesthesia, such as an epidural hematoma or abscess, seems to be larger than that estimated during the past decades: According to Horlocker and Wedel (1998) [10], the incidence of neurologic complications vary from 1 / 220.000 to 1 / 150.000 following spinal and epidural anaesthesia, respectively. In the last few decades, the indications for performing epidural anaesthesia have changed and expanded, patient's characteristics have been modified and of course the awareness of this serious complication has grown; today, it is estimated the incidence of occurrence of serious complications after epidural anaesthesia in non – obstetric patients varies from 1 / 6.000 up to 1 / 1000 cases [13,14]. On the other hand, this complication seems to be much less frequent in procedures performed in obstetric patients, with the incidence of epidural hematoma reported to be in 1 / 154.000 cases [15].

Case presentation

A patient aged 73 with a clear personal health record was admitted at the Department of Scoliosis and Spinal Cord of the Hospital on the 4thday following a Whipple procedure due to sudden onset incomplete paraplegia. The patient received no anticoagulants since he was fully- mobilized on the 2nd postoperative day. Clinical examination did not reveal any pathological findings in the left lower limb, Muscle strength of 0/5 was recorded in the respective right lower limb in all muscle groups, while sensitivity of ½ in the whole area was encountered. Anal sphincter tone was absent and the patient showed signs of saddle-like sensory loss. He urgently underwent a CPEA MRI and a lumbar spine MRI. MRI showed a hematoma in the posterior epidural space extending from T4 to T8. The patient was urgently taken to the operation and underwent, under general anesthesia and in prone position, T4-T8 central laminectomy, as well as drainage of the epidural hematoma.

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Discussion

The spinal epidural hematoma (SEH) occurs in 0.1% to 3% of patients, and is characterized as an event requiring urgent surgical intervention [1,2]. The clinical factors which may impact the outcome are: patients' age and gender, the cause and location of the hematoma (arbitrary, postoperative or post traumatic), the early onset and degree of neurological deficit during treatment, the treatment as well as the availability of postoperative rehabilitation [2]. Patients with medium or mild neurological deficits prior to surgery are most likely to achieve better results from those with complete sensory and motor paraplegia, as well as from those who had been under anticoagulants or presented various comorbidities [2]. Among those who suffered from epidural hematoma and an accompanying neurological disorder, 47% of recorded patients recovered fully, 28% recovered partially and 25% did not show signs of recovery [3].

The main factors determining the long-term outcome were the degree of neurological deficit during treatment and the timing of the surgical intervention (decompression within 12 hours) [2].

The cause of spinal epidural hematomas is an injury to the posterior spinal and epidural vessels (in most of the cases the veins and less often the arteries), during an anaesthetic procedure (drug administration, epidural catheter removal). This hematoma may occur regardless of patient's history of coagulopathy [16]. According to Han et al. (2010) [17], in many cases, a small hematoma is produced forming a clot during the placement of the catheter, which is then dislodged during catheter removal. The volume and the location of the hematoma, as well as the extent of compression of the thecal sac play an important role in the clinical presentation of the neurological deficit [18]; thus, even small bleeds can produce particularly severe symptoms, depending on the local diameter of the spinal sac [19]. Additional risk factors include pre-existing coagulopathy, or anticoagulation therapy, older age, female sex, chronic renal disease, anatomical abnormalities of the lower thoracic and lumbar segment, osteoporosis and usage of large needle size.

The clinical presentation of an epidural hematoma is characterized most of the times by pain in the site of the injury, radiating distally to the extremities, progressing in most of the cases to various degrees of neurologic deficits [21]. Domenicucci et al. (2017) [7] in their case series used a modified Neuro – Grade scale consisting of 4 grades (Grade 0: no deficit, up to Grade 3: paraplegia or tetraplegia) [22] to clinically assess patients at initial presentation and follow–up assessments. The vast majority of the patients (84%) presented with serious neurologic symptomatology (NG score 2-3), whereas only 2% demonstrated NG score 0. The main factors determining a good functional outcome include the severity of the clinical condition and the timing of evacuation of the hematoma (it is evident that the earlier surgical intervention leads to better clinical and functional results, with the optimal time being the first 12 hours after the initiation of the symptoms) [5,23].

The findings of the current literature show that treatment of spinal epidural hematomas remains controversial. According to Domenicucci et al., (2017), [6] the most important, probably, factor which will determine whether the hematoma's treatment will be conservative or surgical, are the laboratory findings regarding the coagulation state of the patient. In all cases, bleeding diathesis should be treated pharmacologically. Surgical intervention should be performed immediately in cases where the neurologic symptoms are severe (for example for grade 2 of the modified Neuro-Grade (NG) scale, meaning para – or tetraparesis [7]), or when there is an obvious clinical deterioration. Characteristic is a case report by Umegaki et al., (2016) [27] of a rapid developed spinal epidural hematoma in a 68 – year old male just 15 minutes after the removal of a spinal epidural catheter, who was treated successfully after an emergent evacuation of the hematoma, which was spreading between T3 – T6, just three hours after the onset of the symptoms. In the present case report, the immediate performed MRI scan which proved the diagnosis of an epidural hematoma between T4 – T8, along with the emergent surgical intervention resulted in the

excellent post-operative outcome.

Conclusions

In the present case surgical intervention was immediate, and that is the reason why the postoperative recovery was smooth. However, this case is particularly interesting due to the delayed onset of the hematoma, the total absence of predisposition factors (no signs of a pre-existing spinal stenosis) to justify its onset, as well as the fact that no anticoagulants had been administered during the first surgery (Whipple).

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ACTA YOUNG SCIENTISTS' PAGES

The Role of Collagen in the Pathogenesis, Pathophysiology and Treatment of Amyotrophic Lateral Sclerosis

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that affects the upper and lower motor neurons and is characterized by progressive paralysis and death from respiratory failure. The genetic heterogeneity of ALS is an obstacle to its diagnosis and treatment. For many years, the only orthodontic treatment for the disease was riluzole. In recent years, a second nosocomial treatment, entaravone, has been approved and used. In the present review, attention is focused on the levels of different collagen classes in patients with ALS. The role of certain forms of collagen that aim at both the pathogenesis and pathophysiology of ALS and in the treatment is presented. The specific characteristics of collagen that may concern us in the future are mentioned, either as biomarkers for the understanding and early diagnosis of the disease, or for new therapeutic approaches.

Key Words: Amyotrophic lateral Sclerosis, Treatment, Collagen

Introduction

Amyotrophic Lateral Sclerosis (ALS) is referred to as "Lou Gehrig's Disease", in honor of the baseball player who was diagnosed with ALS in 1939 and died in 1941, at the rage of 38. It is characterized by progressive paralysis and death from respiratory failure. Although the disease may affect at an early stage only the lower or only the upper motor neuron, in the long run it seems that both are involved. ALS, in most cases (90%) has a sporadic form (sALS), less often (10%) a positive family history is found in patients and is called familial cases (fALS). Epidemiologically, it is estimated that the disease ranges from 1 to 2 new cases per 100,000, per year, while its prevalence is 4 to 6 per 100,000 people. It affects men more often than women and is expressed in the adult phase of life. Life expectancy is quite unstable as it depends on the elation of ALS, however it is defined as 2-3 years from the onset of symptoms. The rate of progression of the disease may be faster in older people. The purpose of this review is the presentation of the data so far, the role of collagen in ALS, both for the prognosis of the disease and for its treatment. A thorough literature search was performed in the PubMed database using

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the key words ''role of collagen in ALS'' and ''role of collagen in neurodegeneration''.

Discussion

The search yielded 83 results in total, which 39 were excluded since they weren't relevant to this review. The full text articles of the remaining 44 records were then investigated for eligibility and 11 of those were excluded for various reasons, leaving 11 articles for the synthesis of this review. Finally, 5 articles were included which were identified from the literature of other researches (Figure 1).

Pathogenesis & Pathophysiology of ALS

Early diagnosis is an important role for the control and possible treatment of the disease, but the complexity of the mechanisms of action and the ambiguity of the symptoms has not allowed the existence of effective diagnostic tests to date. Often, patients experience muscle weakness, contractions and cramps resulting in problems in the muscles. At a more advanced stage they may experience more serious problems such as shortness of breath and dysphagia. The classification categories of ALS include: (a) Progressive Muscle Atrophy (PMA), (b) Progressive muscle paralysis (PBP), (c) Primary Lateral Sclerosis (PLS) and (d) Pseudopromic palsy. More than 50% of cases have cognitive function problems, while more than 13% are associated with frontotemporal dementia. As far as diagnostic criteria are concerned, the World Federation of Neurology, announced for the first time, in 1994, the so-called El Escorial, criteria that were revised and upgraded in 2000, taking the name Airle House. We arrive at 2008, where a new addition is made, the Awaji electrophysiological criteria, with the aim of diagnosing ALS at as early a stage as possible. The pathogenesis of ALS is not entirely clear, it remains unknown. There are several possible mechanisms associated with neurodegeneration, characteristic of the disease. ALS can be inherited in an autosomal dominant way, recessive or sex-linked. The main genes associated with the onset of ALS include: (a) superoxide Dismutase (SOD1), a cytoplasmic protein that breaks down peroxide roots and is involved in oxidative phosphorylation (3). Mutations in the SOD1 gene have been identified in about 20% of the familial and in about 1–4% of sporadic ALS cases (6). Localized mechanisms of action are incorrect folding and aggregation of proteins, oxidative stress, mitochondrial or axial dysfunction, a metabolic disorder through microglia as well as through cell apoptosis(7,8), (b) TARDBP and FUS are involved in the processing of RNA, reinforcing the hypothesis that disturbances in RNA metabolism can cause ALS. The first encodes the TDP-43 protein and has been identified at 0.7–2% in sporadic ALS and 4–6% in familial ALS cases, while the FUS gene encodes the sarcoma fusion protein and has been identified in 4% of familial and 1% of sporadic cases(3), (c) C9orf72, which is involved in the processes of intracellosis and autophagy(3,6). It has been identified by 40% in family cases and about 7% in the sporadic form of ALS.

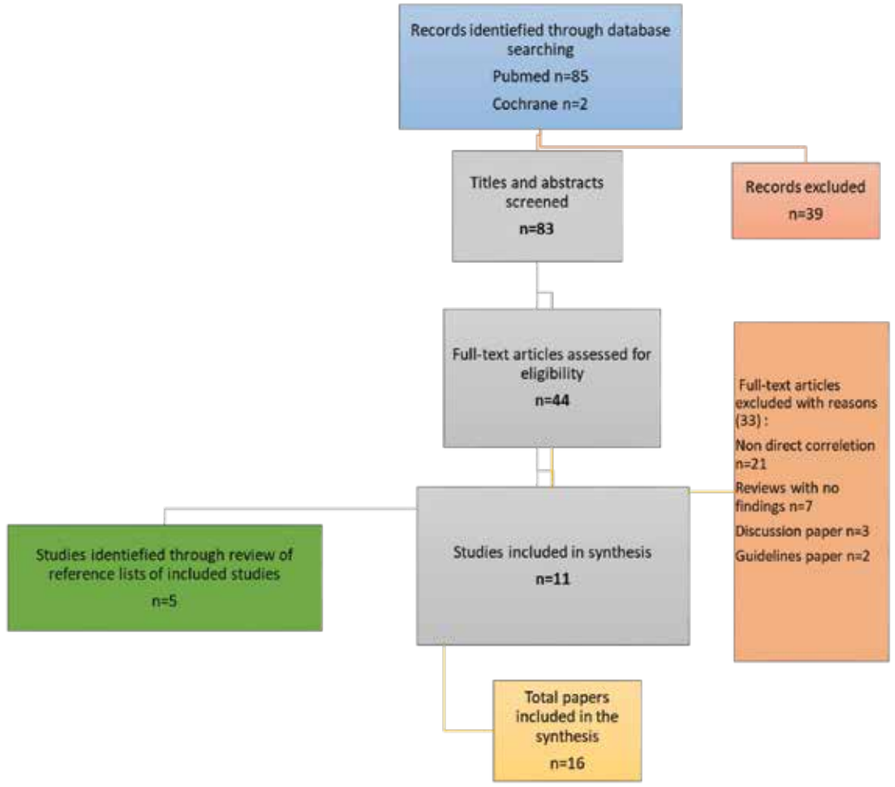
To date, no effective treatment has been found, however, techniques are applied to slow the progression of the disease. For several years, riluzole extended survivorship in patients with ALS, mainly with pseudoprometic form of ALS. The pathophysiological mechanism is not fully known. It is thought to presynaptically inhibit the release of glutamic acid and increase its reuptake from the presynaptic endings. It acts as an indirect antagonist of glutamic acid and prevents its metasynaptic action, possibly interacting with the taseo-dependent sodium channels, stabilizing them in inactive form or with G-proteins. In this way it protects against overstimulation toxicity. Each patient follows various tactics and methods of slowing down symptoms, such as respiratory support that includes tracheostomy and non-invasive support, muscle relaxant treatment, physiotherapy exercises, use of gastrostomy in patients with dysphagia and administration of analgesic drugs. In 2017, the FDA approved entaravone (edaravone), a neuroprotective drug acting on CNS, as an antioxidant. Its mechanism of action remains unknown, however it seems to neutralize the free radicals of peroxide and hydroxyl in motor neurons. Other treatment options are still under study, including the chemical compound NU-9, stem cells as well as the effect of collagen.

Role of collagen

The most abundant fibrous proteins that are widespread in the extracellular space of all vertebrate tissues and other organisms are members of the collagen family. Collagen is the most abundant protein of our body. It provides the necessary structural integrity to the tissues, while regulating a variety of physiological functions. To date, approximately 28 genetically different types of collagen have been identified in vertebrates with various structural and biochemical characteristics. It is the main fibrous component of the skin, tendons, bones, cartilage, vessels and teeth. Its role in the organization is basically structural. It gives strength and maintains the integrity of the structure of connective tissue and organs of the body. It is found within the connective tissue not as an isolated molecule, but as a component of the complex system of tissue, which includes various other macromolecules such as elastin, glycoproteins and glycolipids. It serves to hold cells in distinct functional cell groups. Based on the function and homology of their sequence, several categories of collagen can be distinguished: (a) fibrin (types I, II, III, V, XI, XXIV and XXVII), (b) those forming networks (types IV, VIII and X), (c) those that form adhesion microfiberides (type VI), (d) those attached to fibrils with intermittent triple helix, known as FACIT (types IX, XII, XIV, XVI and XIX), (e) those characterized by multiple helical segments and interruptions and are called multiplexins (XV and XVIII). The role of collagen is not limited only to the maintenance of the structural integrity of tissues and organs. As a component of the basic membranes it acts as a molecular filter of substances. The interaction of collagen with agents, such as integrins, glycoproteins or specialized proteoglycan receptors, determines the differentiation, growth, adhesion, as well as the survival of cells. It binds growth factors and cytokines, as a result of which it plays a role in the development of organs, wound healing and tissue repair. Noteworthy is its application as a biomaterial in tissue mechanics, which aims at the regeneration, repair and replacement of human tissues for the treatment of diseases. Collagen is used in the manufacture of porous scaffolding, a three-dimensional construction that provides the necessary support for cells to attach, multiply and maintain their function. Its physical characteristics, combined with its biocompatibility and low immunogenicity, make it an excellent biomaterial. Its polypeptide skeleton contains many functional groups, facilitating access to genes, growth factors and other biological molecules. The type of collagen that is most used in tissue engineering is the one that is most abundant in the human body and has been studied the most, it is type I collagen. It is the most commonly occurring type in the upper vertebrates since about 80% of the collagen in the body consists of types I, II and III. It constitutes 90-95 % of the organic mass of bone and tendon and is the main type of collagen tissues, such as the skin, cornea, joints, dentin and arteries. Most connective tissues also contain this type of collagen, in addition to the vitreous cartilage, the brain and the vitreous fluid of the eye. Type I collagen is mainly composed in a large percentage of fibroblasts, osteoblasts and odontoblasts and in a smaller percentage some other types of cells present in tissues. The main role of type I collagen is structural, while it plays an important role in the proper development of tissues and organs. The collagen fibers of type I determine the shape and mechanical properties of the tissues, giving them the necessary stiffness and tensile potential. It contributes to the necessary hardness and endurance of the bone. The characteristic structure of the fibers of type I collagen is also important for the tendons that connect the muscles with the bones, as it offers them the possibility of more complex movements. It is involved in the healing process of wounds and fractures, and the processes that inhibit the synthesis of collagen delay their healing. Mutations in the genes encoding the triple helix chains of type I collagen or the proteins involved in the modifications of collagen during its biosynthesis can lead to various diseases. Collagen types I and III appear in a high concentration on the skin. It seems that collagen fibril diameter has a decreasing trend in ALS patients, is related to the pathogenesis of the disease but also has a direct relationship with the involvement of motor neurons. This degeneration is proportional to the length of time patients have been suffering. The fragmented and widely separated bundles of collagen in the tissue surrounding the capillaries and the markedly reduced amount of collagen in the posterior and anterior horn may be associated with the degeneration of upper and lower motor neurons in the spinal cord in ALS. The review, in addition, analyses the role of types IV, V, VI and XV, in the Peripheral Nervous System (PNS)

Figure 1.

Flow diagram showcasing the results of a search in the PubMed database and the selection process for the articles used in this review



in ALS patients. Collagen depletion brings changes in myelin levels and Schwann cells. Degradation of myelin makes it more difficult to transport impulses and thus either upper or lower motor neurons are affected. Of course, such information helps us to compensate for the appropriate types of collagen for functional nerve repair in people with ALS. Collagen VI is a peculiar component of the collagen superfamily made of 3 genetically distinct chains and abundantly deposited in the basement membrane of a variety of tissues, such as skeletal muscles skin, and peripheral nerves. It contributes to the structural integrity and physiological functions of peripheral nerve. Collagen VI regulates myelin thickness by modulating myelination-related signaling pathways. A proper thickness of myelin is required for the correct transmission of electrical impulses along the axons and preservation of axonal integrity in PNS. It is considered as a cell pro-survival factor, since collagen VI deficiency induces muscle cell apoptosis and enhances neuron death on toxic

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treatments in CNS.

Role of Collagen XIX

Finally, interest is turning to type XIX collagen, and this is because its levels are now typically elevated in ALS patients. This allows a more robust prognosis, especially in people who have shown the first symptoms. It has already become clear that there is a close relationship between ALS and COL19A1, which is now a predictive biomarker of the disease. Studies are being conducted on the role of type XIX collagen in terms of its importance in motor neuron degeneration for any disease in this category. Type XIX collagen is a building block of the basement membrane, a specialized extracellular matrix in vertebrates and some invertebrates. These membranes are present in the epithelium, connective tissue, blood vessel walls, axons, adipocytes, and muscle tissue. In addition, they present a dual functionality: on the one hand, these membranes maintain the tissue architecture, and on the other hand, they can regulate biological functions in contact with other cells by means of adaptive proteins. In this sense, they will play a task in cell migration, adhesion, differentiation, proliferation and taxis (Oudart et al., 2017). Although type XIX collagen was first identified in rhabdomyosarcoma cDNA clones, immunohistochemical analysis provided a wider distribution of this collagen in different human and muscle tissues, such as breast, colon, kidney, liver, placenta, cerebellum, prostate, cortex and hippocampus), skin and spleen (Sumiyoshi et al., 2001; Myers et al., 2003; Su et al., 2010; Oudart et al., 2017). Despite, the transcription and protein levels of type XIX Collagen (COL19A1) not only varies from embryonic to adult in some tissues, but also gradually decreases after birth, except in the brain where Col19a1 gene expression is ten times larger in adult mice than in embryonic mice condition (Sumiyoshi et al., 1997). Since its discovery in 1992, type XIX collagen has attracted attention among members of the FACIT family. To date, 42 genes encoding 46 different α chains have been identified in this collagen superfamily, which represents about 30% of the total protein weight in mammals and is also present in all invertebrate plants. (Brown and Timpl, 1995; Oudart et al., 2017).All of these family members share a triple helix consisting of three polypeptide segments aligned in parallel and their exclusive localization in extracellular matrices (Brown and Timpl, 1995). The main fact is that most of the α chains can contain several non-triple helical protein units, which gives more unit diversity than any other family of proteins as they are unique to this family or can be shared by other extracellular proteins (Brown and Timpl, 1995). These collagens are involved in the integrity and stability of the extracellular matrix, regulating the formation and size of collagen fibers and controlling cellular organization in the extracellular matrix (Oudart et al., 2017). Their specific localization in certain tissues and the fine-tuning of their expression make the members of the FACIT family key targets for understanding functional alterations in different cells and organs. In fact, type XIX collagen was discovered by a human rhabdomyosarcoma cell line (CCL-36) (Brown and Timpl, 1995; Oudart et al., 2017). The exact functions of this collagen are still unclear, although it is known to be involved in the formation and maintenance of the extracellular matrix, especially during the embryonic stage. In contrast, the biochemical characterization and chromosomal location of type XIX collagen have been analyzed in depth.

Conclusion

ALS is a rare and neurodegenerative disease, during which degeneration and death of motor neurons takes place step by step (Calvo et al., 2014; Al-Chalabi et al., 2016). In accordance with the Awaji criteria, each the higher motor neurons and therefore the lower motor neurons degenerate or die in ALS, and as a consequence communication between vegetative cell and muscle is lost, prompting progressive muscle weakening and therefore the look of fasciculations. From a diagnostic purpose of read, the analysis of the primary steps of ALS identification is troublesome since there's a large vary of neuron diseases that share its common and heterogeneous symptoms (Burgunder et al., 2011). Concerning ALS, the dysfunction and loss of each higher and lower motor-neurons beside gradual jerkiness could also be gift within the weakened limb, poignant sleight and gait though there ought to be no involuntary, sensory, or psychological feature involvement (Vucic and Kiernan, 2009). Therefore, the necessity of distinguishing reliable diagnostic or

prognostic biomarkers in ALS is AN increasing field of analysis. This study was designed and performed to spot the role of scleroprotein for ALS malady progression that might be in shut reference to the clinical parameters for a much better observance and stratification of the patients. The start line during this study was the muscle tissue though we tend to additionally explored blood tissue to spot and validate prognostic biomarkers in an exceedingly non-invasive manner. High levels of COL19A1 might act as a countervailing response once the malady progression is quick, that is in accordance with previous studies that urged a detailed relationship between COL19A1 factor and ALS in muscle biopsies from ALS patients. These findings unconcealed the potential use of COL19A1 to boost prognosis within the malady progression in an exceedingly non-invasive manner. the mixture of high COL19A1 expression levels and a quicker malady progression will promote a shorter life in ALS patients, and so COL19A1 levels may be thought of a reliable blood-derived biomarker in muscle biopsies and in blood to support the clinical apply and to be of facilitate in future clinical trials, further as a promising and novel therapeutic target in ALS.

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Static Balance Rehabilitation in Individuals with Incomplete Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) is damage to the tight bundle of cells and nerves that send and receive signals from the brain to and from the rest of the body. SCI can be caused by direct injury to the spinal cord itself or from damage to the tissue and bones that surround it. Patients with SCI often experience motor, sensory and/or respiratory dysfunction, as well as bladder, bowel and/or sexual dysfunction. An incomplete injury means that the spinal cord is still able to transmit certain messages to and from the brain to the rest of the body. Balance dysfunctions are one of the most prevalent impairments post incomplete SCI (iSCI). Static balance is also one of the major determinants of walking function; therefore, discovering effective strategies to improve static balance in this population is significant.

The purpose of this review is to highlight the importance of static balance rehabilitation in individuals with iSCI, as well as to describe effective modes of balance training in this population.

Key Words: static balance, balance impairment, balance training, rehabilitation, incomplete spinal cord injury

Introduction

SCI is a complex condition that disrupts a person's life. According to the World Health Organization (WHO), SCI is defined as damage to the spinal cord, including the conus medullaris and the cauda equina, which causes temporary or permanent changes in its function. Estimated annual global incidence, although there is no reliable estimate of global prevalence, is 40 to 80 cases per million population. Up to 90% of these cases are due to traumatic causes, though the proportion of non-traumatic SCI appears to be growing [1].

Approximately 60% of individuals with SCI suffer an incomplete lesion [2]. Individuals with iSCI often develop impairments in muscle strength, sensation, and abnormal muscle tone, making it challenging for them to recover balance function [3]. Among those with iSCI, about 75% will experience at least one fall each year, while standing and walking [4]. Falls can cause fractures, soft tissue injuries, fear of falling, subsequent restriction of activities and community participation. Balance dysfunction is one of the major factors leading to impaired mobility and postural control, affects walking ability and influences balance control in daily life [5,6].

Good balance requires the coordination of muscles and nervous system. The afferent sensory information received through the proprioceptive, visual, and vestibular systems is an important factor for balance control [7-9]. Impairment in one system can lead to higher reliance on the other systems. However, static balance training is often ignored during rehabilitation of patients with iSCI. Therefore, including effective physiotherapeutic strategies to improve static balance in rehabilitation program of individuals with iSCI is important.

PubMed, BioMed central and Cochrane library databases were searched for studies published between 2002 and 2022 using keywords such as, "balance training" and "incomplete spinal cord injury". Our literature research was completed in June 2022 and the review was carried out according to the guidelines of the PRISMA (12).

Eligibility criteria: Studies providing information on outcome measures and prognostic factors about recovery from balance impairment after iSCI. The articles had to be either written or translated into English. Access to full text was essential.

Study exclusion criteria:Articles that were not written or translated in English were excluded. Articles that were impossible to be accessed in full text were excluded as well. Articles that were case studies were also excluded.

Each record that met the inclusion criteria was fully read and 44 reports were retrieved by the reviewer (Figure 1).

Discussion

The initial electronic database search resulted in a total of 66 articles, of these, 44 were considered for inclusion in this review (Figure 1).

The rehabilitation of patients with SCI is multidisciplinary and comprises multiple aspects [10]. A detailed clinical assessment is significant to set adequate rehabilitation goals. All therapeutic interventions should be monitored with adequate outcome measures [11]. In this section, effective physiotherapeutic approaches of balance training are describedthat aim to modifybalanceand the risk for falls by means of therapeutic exercises, assistive devices like robots or functional electric stimulation, and environmental adaptations in individuals with iSCI.

Strength Training: Observational studies investigating balance issues report that the rehabilitation program should focus on increasing muscle strength of the trunk and lower extremities. For this reason, a physical performance test must be conducted in order to determine the adequate dosage [12].

Locomotor Training: Locomotor training is an activity-based therapeutic intervention whose goal is to activate the neuromuscular system below the level of the lesion to promote recovery of motor function with the purpose of retraining the nervous system to recover a specific task. Activation of the neuromuscular system occurs during repetitive and progressive practice of the desired task; "activity-dependent plasticity" promotes functional reorganization of the neuromuscular system [13,14].

Results of the study of Harkema et al. in 2012 showed that significant functional recovery can occur months to years after iSCI with rehabilitation that involves intensive activity-based therapy. Significant improvements in balancewere observed when locomotor training was delivered as a standardized therapy to individuals with clinically iSCI across seven rehabilitation centers. Patients with AIS grades C and D significantly improved in overall Berg Balance Scale (BBS) scores, indicating better functional ability during sitting or standing. These improvements in overall BBS scores likely responded to the intense retraining of standing and stepping, as well as integration of the practice of sitting and transitional movements in their daily lives [15].

In addition to this, Lotter et al., in 2020, observed gains in balance confidence following task-specific vs

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impairment-based training, although incidence of falls was also increased with the former protocol. This study delineates the effects of specificity of rehabilitation interventions on locomotor function in patients with motor iSCI, revealing greater walking improvements and balance confidence following stepping versus impairment-based practice [16].

Overground Locomotor Training (OLT): In 2019, Neville et al. demonstrated improvements in balance and gait using a task-specific, performance-based OLT for chronic iSCI. Interventions included two 90-minute OLT sessions per week over 12 to 15 weeks. OLT sessions were built on three principles of motor learning: practice variability, task specificity, and progressive overload. Training used only voluntary movements without any form of support or facilitation. Subjects used only ambulatory assistive devices as required [17].

Body Weight-Supported Treadmill Training (BWSTT):BWSTT allows for the repetitive practice of walking or stepping in a controlled environment in which the individual's weight is partially unloaded and sensory input is provided facilitating normal walking parameters. A harness supports patients' body weight and provides more support than a gait aid [18]. Alexeeva et al., in 2011, compared two forms of device-specific training – body-weight-supported (BWS) ambulation on a fixed track (TRK) and BWS ambulation on a treadmill (TM) to comprehensive physical therapy (PT) for improving walking speed, in persons with chronic, motor-iSCI. A significant improvement in balance was seen only for PT and TRK groups. The results demonstrated that persons with chronic, motor-iSCI can improve walking ability following a concentrated period of ambulation therapy, regardless of training method. Improvement in walking speed was associated with improved balance and muscle strength [19].

Intensive Mobility Training (IMT) is a treatment paradigm that merges BWSTT and massed/intensive delivery of therapy into one cohesive rehabilitative approach. In the study of Fritz et al, participants received IMT three hours per day, 3-5 days per week for 10 days, for a total of 30 hours. Each session devoted a third of the time to therapeutic interventions focused on improving balance, a third to locomotor training with body weight support system, and a third to activities designed to improve muscle coordination, strength, and range of motion. IMT resulted in larger effect sizes for balance and mobility than for gait in individuals with chronic iSCI [20].

In 2018, Martinez et al. showed that for patients with chronic iSCI, a multimodal exercise rehabilitation program incorporating balance exercises with skilled upper extremity exercises showed no benefit compared to an active control program of BWSTT [21].

Robot-Assisted Gait Training (RAGT): RAGT is an exoskeletal-type robot (Lokomat®) with a treadmill base. RAGT allows the patient to safely experience physiological gait patterns with body weight support by a harness. At the same time, an end-effector type robot is used in the clinical field. On the one hand, the exoskeletal-type robot links the ankle, knee, and hip joints to the robot. On the other hand, the end-effector robot attaches only the feet to the footplate, and consequently it allows free movement of the knee and hip joints. This "destabilization training" provided can reinforce the neuronal circuit and contribute to postural control and sensory integration. RAGT in patients with iSCI revealed improvements in mobility-related outcomesand lower extremity motor strength compared to conventional physiotherapy [18].

Nam et al. observed significantly greater improvements in balance in the chronic RAGT groups, compared to the no intervention groups, in patients with chronic SCI. However, no trial with acute participants measured recovery of balance. The acute RAGT groups showed significantly greater improvements in gait distance, leg strength and functional level of mobility and independence than the OLTgroups.Thus, RAGT improves mobility-related outcomes to a greater degree than conventional OLT for patients with iSCI, particularly during the acute stage [22].

However, according to the study of Alashram et al., there is insufficient evidence for the effects of the Lokomat on balance in people with iSCI [23]. Piira et al. reported a significant improvement in the BBS scores after Lokomat training compared to the usual care-control group. The sample size was small; hence, the clinical effects cannot be confirmed [24]. The study of Shahin et al. reported improvements in the BBS scores after RAGT and conventional physical therapy (CPT) experimental and the CPT control interventions, with no significant differences between groups [25]. Labruyere and van Hedel did not show significant differences between groups in the BBS, the Figure Eight Test (FET) and the Falls Efficacy Scale-International Version I (FES-I) scores [26].

In the study of Shin et al., participants received RAGT with Morning Walk® (Curexo, Seoul, South Korea). This is an end-effector type robot which uses a saddle for weight support. All clinical outcomes showed a significant improvement after 20 sessions of RAGT. In addition, they evaluated balance ability as an outcome measure that lacks evidence of the effect of an end-effector RAGT in patients with SCI. The results of this study suggest that the end-effector RAGT could act as task-specific, repetitive, and desensitization training to promote proprioception, balance ability, and walking ability [18].

Moreover, Khan et al., in 2019, conducted research with participants with chronic motor complete or incomplete SCI, who were primarily wheelchair users, and were trained to walk in the powered exoskeleton ReWalk for 12 weeks. In the ReWalk, participants learned sit-to-standtransitionsand vice versa, as well as balancing in standing. Sitting balance was improved in some participants, as seen from the limits of stability and sway speed. About 45 sessions of training are required for individuals with severe SCIin order to achieve walking proficiency in the ReWalk. The ReWalk is a promising device to train walking in individuals with severe SCI with good upper extremity strength [27].

Furthermore, in 2020, Calabro et al., proved the efficacy of robot aided ankle rehabilitation, using the platform robot Hunova, in improving gait performance and balance in persons with iSCIby retraining muscle activation and corticomuscular coherence in a framework of preserved motor coordination. The platform robot Hunova allows for functional sensorimotor evaluation and rehabilitation of the ankle, lower limbs, and trunk in both standing and sitting positions [28].

Functional Electrical Stimulation (FES): FES is a subtype of neuromuscular stimulationin which the stimulation assists functional and purposeful movements. This is accomplished by applying electrical stimulation to muscles that, when they contract, produce a movement that can be used functionally. The order in which the muscles contract, as well as the muscles themselves, are specifically selected to produce the desired movement. A FES system that facilitates a specific movement is often referred to as a neuroprosthesis or motor neuroprosthesis [29].

The ability to stand is often affected by SCI. FES can be used to activate the muscles around the ankle joints which, in combination with a support system for the trunk (e.g., a standing frame or a full-body orthosis), can restore the ability to stand. Additionally, stimulation channels can be used to facilitate trunk control. The Case Western Reserve University/Department of Veteran Affairs (CWRU-VA) neuroprosthesis for standing used a 16-channel implanted stimulator. Bilateral activation of the thighs, hip, and trunk allowed a person with paraplegia to stand upright for eight min, when combined with an ankle–foot orthosis [29].

Audu et al. designed and tested a feedback control system for maintaining seated balance under external perturbations in individuals with thoracic and cervical level SCI. The control system relied on a signal related to the tilt of the trunk from the vertical position derived from a sensor fixed to the sternum to activate user's own trunk and hip extensor muscles via an implanted neuroprosthesis. The results support the feasibility of automatically controlling seated balance with FES. Perturbations up to 45% body weight were successfully rejected by the controller. Consequently, such a controller would be helpful for maintaining trunk balance during everyday activities and prevent falls [30].

Houston et al. evaluated a therapeutic tool for standing balance that combined FES, applied bilaterally to the plantarflexors and dorsiflexors, with visual feedback balance training (FES+VFBT). Visual feedback of the COP location was provided as participants completed the balance exercises and received FES to assist with performance of the exercises. Following training, four of five participants showed improvements on at least one of the clinical balance scales, with less impact on balance confidence as measured by the ABC scale. The area of maximal COP excursion increased for all

participants, while there was no significant effect on quiet stance assessments. While most participants did not sustain their improvements at eight weeks post-training, the fact that FES+VFBT was able to elicit improvements in balance ability despite a small training dosage suggests that it is a promising intervention for standing balance rehabilitation among individuals with iSCI [31].

Virtual Reality (VR): VR is a type of interface among user and computer that gains a real-time simulation of activity or environment and allows user interaction via multiple sensory modalities. The VR training activates the cerebral cortex and enhances spatial orientation capacity, hence facilitating the brain cortex to improve the balance ability and improve motor functions. In 2020, Alashram et al. concluded in their systematic review that the influence of VR training on the balance ability in patients with chronic incomplete SCI with C and D on the ASIA scale is promising. In terms of balance, VR training may induce neural plasticity on multiple levels of the central nervous system. They propose that applying 12–20 sessions of 30 to 60 min of VR may show beneficial effects [6].

Besides that, in 2017, An and Park found that semi-immersive VR therapy effectively improves balance and upright mobility function in patients with chronic iSCI. In this study, each subject underwent semi-immersive VR therapy 30 minutes per day, three times a week for six weeks. Semi-immersive VR therapy was provided to stimulate the development of diverse trunk control, multiple directional weight-shifting, agility, and upper-extremity movements in the standing position. Real-time repetitive training through an unpredictable scenario in a virtual environment is considered an effective intervention technique to improve postural adjustment control [32].

Wall et al.in 2015 assessed the effects of virtual reality using the Nintendo™ Wii Fit on balance, gait, and quality of life in ambulatory individuals with iSCI. After playing the Nintendo™ Wii Fit games, subjects demonstrated improved forward and lateral functional reach. At the four-week follow up, subjects were able to maintain the significant changes seen in both outcome measurements. All the Nintendo™ Wii Fit games challenged upright postural stability by requiring the subject to weight shift repetitively in all directions [33].

Additionally, Waliaet al. studied the effectiveness of electrical stimulation-augmented virtual reality training in improving balance in individuals with iSCI. The intervention was delivered as 60-minute sessions, thrice a week for four weeks. Intervention included three phases with kinesiotherapy for 15 min, combination of virtual reality-based balance training and electrical stimulation for 30 min and real-world exercises including movements based on those practiced while engaging in virtual reality tasks for 15 min. This is a protocol which has been designed specifically for iSCI and it is believed that it will result in substantial improvement in standing balance in individuals with iSCI [34].

In the research of Villiger et al., 12 chronic iSCI subjects used a home-based, mobile version of a lower limb VR training system. Movement sensors controlled virtual representations of the legs and feet. The subjects performed home-based training over four weeks, with 16–20 sessions of 30–45 min each. The researchers concluded by ending their study that unsupervised exercises at home with the VR training system led to beneficial functional training effects in subjects with chronic iSCI, suggesting that it may be useful as a neurorehabilitation tool [35].

Visual Feedback: Sayenko et al. showed that individuals with chronic iSCI show improvements in upright static and dynamic postural control after balance training with visual feedback during standing. Participants with chronic motor and sensory iSCI who were able to stand for at least five minutes without any form of assistive device performed the balance training with visual feedback, three days per week, for a total of 12 sessions. They stood on a force platform and were instructed to shift their center of pressure in the indicated directions as represented by a cursor on a monitor [36].

In addition, Tamburella et al. found that visual biofeedback task-specific balance training (vBFB) is effective in improving balance and gait in chronic SCI subjects. Inclusion of vBFB in rehabilitation protocols for chronic SCI subjects effects greater improvements in gait than conventional rehabilitation alone [37].

Reactive Stepping Ability: Reactive balance control describes the ability to recuperate balance after an unexpected balance perturbation and can involve keeping the feet in place or taking one or more steps to increase the size of the base of support. This last strategy is referred to as reactive stepping, which, if compromised, can increase fall risk [38].

Chan et al.in 2020 found that reactive stepping ability of individuals with iSCI (AIS D) is impaired; however, this impairment is not explained by temporal parameters. The findings suggest that reactive stepping should be targeted in the rehabilitation of ambulatory individuals with iSCI [39].

On the other hand, Unger et al, concluded that balance training is beneficial for individuals with iSCI (AIS D), but the addition of manual perturbations (PBT) did not prove advantageous for performance on a measure of reactive stepping ability [40].

Provision of Specific Physical Inputs: In et al. provided evidence that the use of whole-body vibration (WBV) holds promise as a safe and effective intervention to decrease spasticity and improve balance and walking function in individuals with iSCI at the cervical level. The WBV group received 16 minutes of WBV training, twice a day, five days a week for eight weeks. WBV training included four sets of 45 seconds of stimulation and a minute break between each session. Finally, a total of 80 training sessions were provided to each patient. All subjects who performed WBV training had decreased spasticity of the ankle plantar flexors and showed improved balance and walking ability [41].

In 2017, Arora et al. investigated the effect of haptic input via light touch on standing balance of individuals with incomplete iSCI. The results of this study showed that individuals with iSCI improved their standing balance with light touch similar to able-bodied individuals. Without vision, postural sway was reduced to a greater extent in individuals with more intact upper extremities (UE) cutaneous pressure sensation and more impaired lower extremities (LE) proprioception. In addition, individuals with iSCI seemed to rely more on vision for standing balance than able-bodied individuals, confirming previous work [6]. Individuals with and without intact UE sensation responded differently to light touch suggesting that thelevel/extent of injury must be considered. These findings suggest light touch has promise as an intervention for balance impairments in individuals with iSCI, and further research is warranted [9].

Arm Crank Ergometer (ACE) "Spin" Training: In the study of Williams et al., participants completed five weeks of a group ACE "spin" training protocol which featured alterations in resistance and cadence as well as back-supported and unsupported bouts. Participants showed significant improvements in seated balance only when they attempted to sit as still as possible with eyes closed while no effects were seen in static seated balance with eyes open or dynamic seated balance. Static seated balance with eyes closed is a more challenging static balance task than eyes open, and so improvements in this particular condition may indicate the benefits of ACE training. Unsupported ACE was effective in eliciting trunk muscle activity in all participants regardless of injury level. After five weeks of training, participants demonstrated improved static seated balance control with eyes closed. These results indicate that an ACE program with bouts of unsupported cranking may be a beneficial technique to enhance activation of the trunk muscles and improve seated balance control in this population [42].

Aquatic Training: Underwater treadmill training (UTT) is a self-initiated walking intervention which has remained largely unexamined as a means of improving ambulation in individuals with iSCI. Use of water as an unloading medium reduces body weight, thus decreasing strength levels needed to move the lower extremities during self-initiated gait. Other contingent benefits of walking on an underwater treadmill comprise improved balance, increased muscle strength caused by overcoming water resistance and turbulence, generation of muscle activity and gait patterns like those seen in overground walking and enhanced venous return and cardiac preload associated with the effects of hydrostatic pressure in an aquatic environment. Data from the study of Stevens et al. revealed that 8 weeks of UTT improved leg strength, balance, and walking performance in adults with iSCI [43].

Furthermore, Marinho-Buzelli et al. assessed the influence of the aquatic environment on quasi-static posture by measuring COP sway and trunk acceleration parameters after iSCI in water and on land. The results showed that increased COP sway seemed

to reflect the balance and sensorimotor impairments of the participants, especially when standing with eyes closed in water. Most participants reported that water felt like a safer environment in which to stand [44].

Conclusion

The ability to maintain postural stability and balance during static or dynamic (non-walking) tasks is a major impairment following iSCI and is strongly associated with fall risk and reduced participation. Indeed, impaired balance is a primary predictor of locomotor function in the chronic phases following iSCI and training activities directed toward improving postural control are a major focus of traditional rehabilitation strategies. However, discussions have moved away from training compensatory strategies with limited chances of recovery to acknowledgement that specific rehabilitation strategies may be critically important to enhance balance function. Specific interventions have been designed to challenge trunk stability during sitting exercises and progression to standing balance activities, focusing on symmetrical weight bearing using different weight-shifting techniques. Additional sensory inputs may be provided, including altered visual input to increased visual feedback via virtual reality, or provision of specific physical inputs such as vibratory stimuli and haptic input.

To conclude with, the current review was designed to highlight these strategies as determined by pertinent research studies developed during these past decades. The main positive effect of the balance training on postural control in individuals with iSCIshould be associated with the improvement of existing and the development of new motor strategies, sensorimotor integration, and a direct effect of the training on the muscles' functional properties. Further studies are required to verify the results of selected positive studies incorporating circuit and combined training interventions during static balance training in patients with iSCI, including potential comparative efficacy studies utilizing different therapeutic approaches, and further details on amounts, type, frequency, and intensity of practice provided, to ensure patient's effort and volitional engagement.

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Conservative versus Surgical Treatment of Spondylodiscitis

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ABSTRACT

Early diagnosis and aggressive initial treatment are essential for obtaining satisfactory outcomes for patients with spondylodiscitis. However, management strategies are still controversial.
A review was conducted with the aim to compare the results of conservative and surgical treatment of spondylodiscitis patients using the online Pubmed database with the following keywords: ("treatment" OR "management" OR "therapy") AND ("vertebral osteomyelitis" OR "spondylodiscitis" OR "spinal infection" OR "discitis").The search included only prospective or retrospective studies, comparing conservative versus surgical management, in terms of outcome and complications. Initially, after a primary search 407 studies were identified. Finally, 14 studies were included in the review (12 retrospective and 2 prospective).
Literature data support that the initial treatment of spondylodiscitis should be conservative with bed rest, bracing and proper antibiotic treatment lasting for at least 8 weeks. However, in cases of neurological deficit, abscess formation, deformities and failure of conservative management, surgical treatment is required. Although conservative treatment is associated with a higher rate of chronic back pain and long-term deformities, it demonstrates a lower mortality rate in comparison to surgical management. Perioperative complications still remain an issue in surgically treated patients; however, patients' satisfaction and quality of life are higher compared to those of conservatively treated patients, indicating that treatment of spondylodiscitis should be individualized taking into consideration patients' clinical presentation, imaging studies and the virulence of the responsible pathogen.

Key Words: spondylodiscitis; vertebral osteomyelitis; spinal infection;treatment; management

Introduction

Spondylodiscitis accounts for 2-7% of all osteomyelitis cases. It affects mainly elderly immunocompromised patients; however, it can also affect young patients in association with HIV infection, immunodeficiency syndrome and intravenous drug use. The most common pathogenic mechanism is hematogenous spread of microorganisms which may occur in any condition that causes bacteremia, such as urogenital, respiratoryor soft tissue infection. The most common responsible microorganisms are *Staphylococcus aureus* (30-55%), *E. coli*, *Salmonella, Enterococcus, Proteus mirabilis, Pseudomonas aeruginosa* (65% of intravenous drug users), *Streptococcus viridans* and *Staphylococcus*

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epidermidis [1].

Typically, the initial mild symptoms gradually worsen, developing continuous and localized back or neck pain, which is exacerbated during rest, especially at night. Additional symptoms may include muscle spasms, weight loss, lower back, groin or buttock pain, and in advanced stages, symptoms of radiculopathy and myelopathy. Serum inflammation markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are usually increased. While plain X-rays become positive only in the advanced stages of the disease, Magnetic Resonance Imaging (MRI) becomes positive very early in its course and has been established as the imaging method of choice. Lesion biopsy and isolation of the responsible pathogen is highly important and should be attempted in any case. Computed Tomography (CT)-guided biopsy is the method of choice because since it allows sample harvesting [2-4].

Early diagnosis and aggressive conservative or surgical treatment are essential for a satisfactory outcome. The primary goals of management are the isolation of the responsible microorganism, the prevention of bacteremia and sepsis, the elimination of the infection, the long-term pain relief, the prevention or reversal of the neurological deficit, the restoration of spinal stability, the correction of spinal deformity and the prevention of the recurrence of the disease. Initial treatment of bacterial and parasitic infections is usually conservative with bed rest and intravenous administration of antibiotics for at least 4-6 weeks, depending on the extent of the infection and the responsible microorganism. Antibiotic treatment should not be ceased before serum inflammatory markers return to normal. Although bed rest is indicated in the very early stages of treatment, early patient mobilization with the help of a brace is recommended. Basic treatment principles also include improving the patient's diet and immune status as well as treating ectopic infections, for example urinary or respiratory tract infections [2,5,6].

Indications for a shift from conservative to surgical treatment are the persistence or worsening of the infection, despite adequate antibiotic treatment, and the presence of pharmacological side effects, as renal or hepatic impairment, limiting further use of the appropriate antibiotics in the required dosages. Surgical treatment is also indicated in case of progressive spinal deformity and instability, formation of spinal abscess or appearance of neurological signs due to nerve compression. Indeed, spinal cord compression requires urgent surgical intervention. However, it may prove useless if the paralysis has been established for more than 24-36 hours [7].

The key to successful surgical treatment is radical surgical debridement. This has been widely proven in the treatment of tuberculous spondylitis, but it also applies in cases of pyogenic spinal discitis. Anterior approach of the spine and radical surgical debridement and reconstruction of the anterior spinal column using bone graft are indicated in patients with intravertebral abscesses without major bone destruction, deformity and instability. Anterior spinal approach is also effective in decompressing the spinal canal if the anterior spinal elements are involved. Posterior spinal fusion after anterior spinal surgery is indicated in cases with significant kyphotic deformity or after radical surgical debridement and corpectomy at multiple levels. Hardware and grafts for spinal fusion can be used at the site of the infection, provided that radical surgical debridement is fully achieved [1,6-8].

The aim of the current study was to assess and compare the results of conservative and surgical treatment of patients with spondylodiscitis. A review of the current literature was conducted using the online Pubmed database and following the PRISMA Guidelines. Article titles were searchedby using the following keywords: ("treatment" OR "management" OR "therapy") AND ("vertebral osteomyelitis" OR "spondylodiscitis" OR "spinal infection" OR "discitis"). Inclusion criteria were comparative prospective or retrospective studies comparing conservative versus surgical management, in terms of outcome and complications. Studies published in non-English language, non-comparative studies, reviews, case reports and study protocols were excluded from the review. Studies on children and adolescents were also excluded. Initially, 407 studies were identified after a primary search on the online Pubmed database. After screening of titles and abstracts, 302 articles were excluded as inappropriate. From the remaining 105 studies, 91 were rejected for various reasons (figure 1), leaving 14 studies for analysis (12 retrospective and 2 prospective studies).

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Discussion

Pyogenic Spondylodiscitis: A retrospective study by Karadimas *et al*, compared the results of conservative and surgical treatment in 163 patients hospitalized for spondylodiscitis.Seventy patients received conservative treatment, 56 underwent posterior decompression and 37 posterior decompression and stabilization. At one-year follow-up, 11% of patients treated conservatively had to be operated, while no one had developed neurological symptoms. Among patients receiving decompression without stabilization, the reoperation rate was 42%, while 26% had developed neurological symptoms. Among patients receiving combined stabilization and decompression, the reoperation rate was 16%, while 30% had developed neurological symptoms. The authors concluded that conservative treatment was effective in 89% of patients with spondylodiscitis, especially in those with mild clinical symptoms and no neurological signs [9]. Similarly, another retrospective comparative study by Valancius *et al*, including 208 patients, described the results of conservative versus surgical treatment of patients with infectious spondylodiscitis. Conservative treatment with antibiotics and bracing was applied in 91 patients, while 94 patients underwent posterior debridement with or without pedicle screw instrumentation and 23 patients underwent anterior debridement with or without pedicle screw instrumentation. The study results showed that the rate of successful conservative treatment was 87%. The authors concluded that administration of antibiotics and bracing is a safe and effective treatment without any complications [10].

In another retrospective observational cohort study including 27 patients with single-level uncomplicated lower thoracic or lumbar pyogenic spondylodiscitis, Nasto *et al*, compared the application of a standard thoracolumbosacral orthosis rigid bracing for 3–4 months (n=12) with posterior percutaneous pedicle screw spinal instrumentation followed by a soft brace for 4 weeks (n = 15). All patients received resistance-adopted antibiotics. At the 6th months follow-up, patients subjected to surgical treatment reported lower pain scores and improved quality of life. However, no statistically significant differences were found in 9 months follow-up. The authors concluded that surgical treatment did not offer any advantage in healing time over thoracolumbosacral orthosis rigid bracing because infection clearance mainly depends on proper antibiotic administration [11].

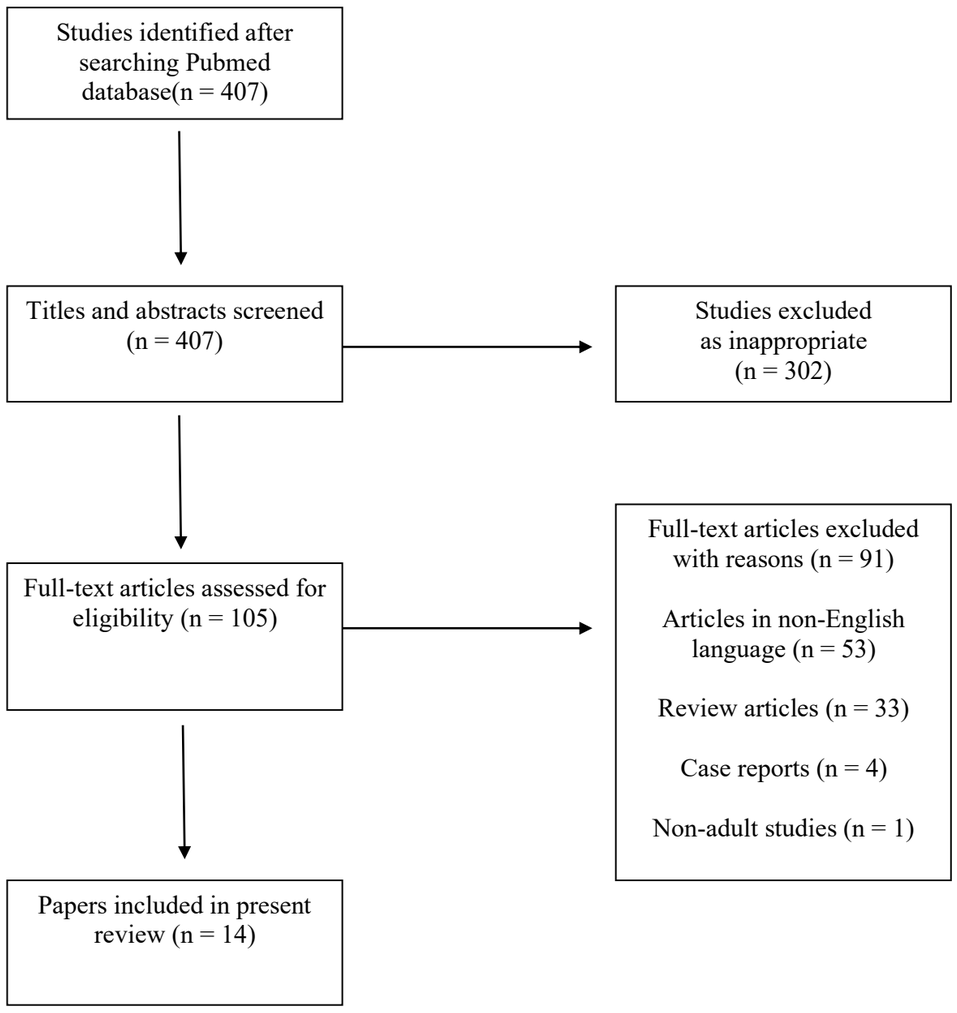
Wirtz *et al*, in a retrospective study, assessed the therapeutic outcomes of 59 patients with lumbar or thoracic spondylodiscitis. Thirty five patients were treated conservatively with bed rest, bracing and proper antibiotics, while 24 patients underwent surgery, due to abscess formation or progressive neurological deterioration. Mean time of immobilization was 5.9 weeks for patients undergoing surgical procedures and 7.8 weeks for patients treated conservatively. The authors concluded that conservative and surgical treatment are not rivals but rather complementary to one another, as they are both indicated for management of spondylodiscitis [12].

A recent, single center, retrospective cohort study by Alas *et al*, enrolled 116 patients with spondylodiscitis. Seventy three patients received only conservative treatment (antimicrobial treatment and analgesics) and 43 patients received surgical plus conservative treatment. Patients treated surgically were significantly younger and less frail. Surgical treatment was significantly associated with decreased 30-day and 1-year mortality rate in comparison to conservative treatment, while an increased frailty index was associated with higher short-term mortality, regardless of intervention [13].

A small prospective study by Waheed et *al*, enrolled 44 patients with spontaneous spondylodiscitis. Twelve patients received conservative treatment with bed rest, bracing and proper antibiotics, 10 patients underwent laminectomy, debridement and open biopsy and 22 patients underwent laminectomy and fusion. The authors concluded that once diagnosis is confirmed, early and prolonged administration of proper antibiotics is recommended for the treatment of spontaneous spondylodiscitis [14].

Quality of life after surgical and conservative treatment of spondylodiscitis was evaluated in a recent, retrospective, single-center study by Behmanesh *et al*. From 210 patients with spondylodiscitis, 155 underwent a surgical procedure and 55 were treated conservatively. Patients treated surgically reported a

Figure 1. Study flowchart



significantly improved quality of life in comparison to conservatively managed patients [15]. A similar study by Woertgen et *al*, retrospectively investigated 62 patients with pyogenic spinal infection. Among them, 28 patients underwent conservative management and 34 patients were operated. Patients treated with a surgical procedure reported a slightly better quality of life and self-reported satisfaction levels [16].

Hematogenous pyogenic vertebral osteomyelitis: A recent retrospective study by Canoui *et al*, evaluated conservative and surgical treatment in 90 patients with hematogenous pyogenic vertebral osteomyelitis. Of those, 69% (n=62) were treated conservatively, while 31% (n=28) received a combination of conservative and operative treatment. At 4-months follow up, although there was no difference in neurological

improvement between the two groups, patients treated both surgically and conservatively experienced less pain. However, at one-year follow up, there was no difference in infection-related complications between the two groups [17].

In another retrospective study, Hadjipavlou *et al,* compared the conservative and operative management among 101 patients with hematogenous pyogenic vertebral osteomyelitis. All patients received antibiotics, initially intravenously and then orally. Sixty-six patients received an operation, while the rest were treated conservatively. Among patients treated conservatively, 64.3% continued to report chronic back pain. In the surgically treated group, only 26.3% of the patients reported chronic back pain at disabling levels. The authors concluded that treatment outcome depends on the type of infection and the severity of neurologic involvement prior to treatment. Conservative treatment may control the infection; however, surgery may prevent deformities and chronic back pain [18].

The therapeutic outcomes of hematogenous vertebral osteomyelitis caused by methicillin-resistant Staphylococcus *aureus* were evaluated in a prospective cohort study by Park *et al*. All of the 139 patients received intravenous antibiotics as an initial treatment, for a mean duration of 50 days. Surgical debridement was performed in 40 patients and CT-guided aspiration drainage was performed in 38 patients. At multivariate analysis, surgical debridement was associated with prolonged hospitalization; whilelonger duration of antibiotic therapy was associated with lower relapse rates [19].

A retrospective multicentre study by Colmenero *et al*, included 219 adult patients with vertebral osteomyelitis. Of those, 48% (n=105) had brucellar osteomyelitis, 33% (n=72) pyogenic and 19% (n=42) tuberculous osteomyelitis. Among them, 119 patients received only conservative treatment and 100 patients received both conservative and surgical treatment. The outcomes of operated patients did not differ significantly from patients treated conservatively, although the mean duration of hospitalization was significantly higher in the group of operated patients [20].

HIV-infected patients: In 2009, Sobottke *et al*, conducted a multicenter retrospective study comparing the outcome of surgical versus conservative treatment in HIV (+) patients with spondylodiscitis. The study included 20 patients; 10 were treated conservatively with antimicrobial agents and 10 received operation. The authors concluded that surgical management of spondylodiscitis in HIV (+) patients is not associated with increased surgical complication rate. As increased perioperative morbidity is not expected, HIV infection should not affect decision-making regarding conservative or surgical management of spondylodiscitis [21].

Elderly patients: A retrospective case series by Sobottke *et al*, compared conservative and operative treatment of spondylodiscitis in patients over 65 years of age. Sixteen patients were managed conservatively and 16 patients were managed surgically. Neurologic deficit, sepsis, instability, abscess formation and impending deformities were indications for surgery, while conservative treatment was applied in patients with mild symptoms. The authors found that the complication rate of surgical treatment of elderly patients with spondylodiscitis was not higher than that observed in younger patients. No difference was also found regarding pain and quality of life; however, satisfaction was higher in elderly patients receiving operation. The authors concluded that age should not influence the decision making regarding conservative or surgical treatment of patients with spondylodiscitis [22].

In conclusion, initial conservative treatment of uncomplicated spondylodiscitis with bed rest, bracing and proper antibiotics for at least 8 weeks, remains the gold standard. However, in cases of neurological deficit, abscess formation, deformities, and failure of conservative treatment, surgical treatment is required. Conservative treatment is associated with a higher rate of chronic back pain and long-term spinal deformities; however, it is also associated with a lower mortality rate in comparison to surgical treatment. Perioperative complications still remain an issue in surgically treated patients; however, patients' satisfaction and quality of life seems to be higher for those patients, indicating that treatment of spondylodiscitis should be individualized taking into consideration patients' clinical presentation and imaging studies and the virulence of the responsible pathogen.

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Bladder and Bowel Dysfunction in Patients with Spinal Cord Injury – Nursing Intervention

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ABSTRACT

Spinal cord injury (SCI) has severe consequences on patients' mobility and body organ function. In particular, its effects on bladder and bowel have been thoroughly studied since, in addition to their adverse effect on patients' quality of life, they are also associated with increased mortality.

The aim of this study is to review therapeutic interventions for the management of bladder and bowel disorders in SCI patients, focusing on the nursing role, as a member of the rehabilitation team in the acute and chronic phase of injury. This is a narrative literature review using the Pubmed internet database. Papers were searched with the use of the following keywords: ("neurogenic bladder" OR "neurogenic bowel") AND "spinal cord injury". Among the 214 publications evaluated, 124 were rejected, leaving 90 studies for the present review.

Treatment modalities in SCI patients with neurogenic bladder include clean intermittent catheterization, indwelling catheters, bladder function training and assisted bladder emptying. Neurogenic bowel may be treated with adequate and appropriate intake of food and fluids, use of dietary supplements and oral medications, selection of appropriate methods to aid defecation and emptying and colostomy surgery. The role of nursing care is of vital importance as it can prevent further injury and contribute to improvement of patients' quality of life.

Key Words: "neurogenic bladder", "neurogenic bowel", "spinal cord injury".

Introduction

Spinal cord injury (SCI) has severe consequences not only for patients' mobility and sensation but also for the function of body organs. In particular, its effects on bladder and bowel have been thoroughly studied since, in addition to their adverse effect on patients' quality of life, they are also associated with increased mortality. Chronic kidney disease is the leading cause of death in SCI patients.

Loss of normal bladder function is one of the most important consequences for SCI patients. Inadequate management of bladder function may lead to complications such as urinary tract infections, urinary retention, incontinence, kidney stones and urinary reflux as well as life-threatening conditions, such as renal failure. Dysfunction of the urinary system following traumatic SCI is determined by bladder dysfunction. The type of subsequent neurogenic bladder depends on the level of SCI, the nature of the lesion (complete or incomplete SCI), as well as

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the time elapsed from injury [2]. During spinal shock phase, the bladder loses its reflexes, the detrusor is acontractile and the sphincters are contracted, leading to acute urinary retention and overflow incontinence. Neuroplasticity progressively alters the properties of bladder afferences and spinal circuitry. A few weeks after injury, areas of spinal cord that were not damaged begin to gradually regain function. During storage phase, the bladder spontaneously contracts (neurogenic detrusor overactivity) leading to decreased bladder capacity, urinary incontinence and vesico-ureteral reflux. During micturition, coordination between detrusor contraction and sphincter relaxation fails (detrusor sphincter dyssynergia), resulting in high detrusor pressure and dysuria. Patients are at the same time incontinent and suffer from chronic urinary retention due to the functional obstruction by dyssynergia. Voluntary bladder control is abolished, while the amount of urine retained in the bladder is large (but not as much as the remaining amount of urine in the immediate post-traumatic phase). Neurogenic detrusor overactivity can trigger autonomic dysreflexia and can impair quality of life [3-4]. As the absence of spinal reflexes subsides, two main types of bladder condition develop: hyperactive (spastic) bladder and inactive (loose) bladder.

Another serious condition in SCI patients is the neurogenic bowel, which is responsible for a large number of gastrointestinal problems, such as decreased motility of the bowel, prolonged passage of contents, chronic constipation, abdominal distension and fecal incontinence. Patients with neurogenic bowel are constantly alert, due to possible incontinence, which negatively contributes to patients' return to previous activities. If not treated appropriately, neurogenic bowel dysfunction results in complications such as irregular bowel evacuation, hemorrhoids, constipation, nausea, pain, ileus, and autonomic dysreflexia [5].

The aim of this study is to review the therapeutic interventions for the management of bladder and bowel disorders in SCI patients with focus on the role of the nurse as a member of the rehabilitation team, in the acute and chronic phase of the injury.

A literature review was conducted using the Pubmed internet database. Papers were searched with the use of the following keywords: ("neurogenic bladder" OR "neurogenic bowel") AND "spinal cord injury". The search was limited to papers published in the last 5 years (2017–2022). Studies in non-English language, case reports, study protocols, pilot studies, animal studies and not nurse – related studies were excluded.

Discussion

The search retrieved a total of 366 papers (Figure 1). After screening of titles and abstracts, 152 articles were rejected as they were not related with the study. Among the 214 publications evaluated, 124 were rejected, leaving 90 studies for the present review.

Neurogenic Bladder - Diagnostic Approach

Normal function of the lower urinary tract is based on a complex interaction between sensory and motor nervous systems. The type of dysfunction should always be identified. A complete medical history, physical examination and an urination diary are required before any other diagnostic tests. The results of the initial evaluation are used to assess long-term treatment [6]. Evaluating patients' present and expected quality of life is important to evaluate the treatment effectiveness. The type of bladder management has been shown to affect health-related quality in SCI patients [7-9].

In addition to patient's detailed history, special attention should be paid to physical and mental disabilities. Patients with high SCIs can cause a significant drop in blood pressure when moved to a sitting or standing position. The sensation and reflexes of the urogenital system must be checked. In addition, the rectal sphincter and pelvic floor function should be checked [7-8].

For the members of the rehabilitation team, ultrasonography is the preferred method for the surveillance of the upper urinary tract dysfunction. Urodynamic evaluation, along with multichannel urodynamics, voiding cystourethrography combined with urodynamics and video-urodynamics are the applied methods that can objectively assess the function of the lower urinary tract [8,10-11].

Principles of Neurogenic Bladder Treatment

Treatment of neurogenic bladder in SCI patients includes new strategies for neurogenic detrusor overactivity, new surgical techniques, prevention of recurrent urinary tract infections [12]. The primary goals for the treatment of neurogenic bladder are: protection of the upper urinary system, achieving (or maintaining) restraint of urination, restoration of the operation of the lower urinary tract and improving patients' quality of life [9,13]. In SCI patients, non-invasive medical management is important to improve urodynamic parameters of bladder capacity, decrease detrusor pressure and improve quality of life outcomes with neurogenic bladder management [6,14-15]. Co-existing neurogenic bowel and spasticity are factors associated with neurogenic bladder [16,17]. Management of neurogenic bladder in SCI patients includes the following approaches: (a) intermittent bladder catheterization, (b) indwelling catheters, (c) condom catheter drainage, (d) assisted bladder emptying, (e) oral drug therapy, botulinum toxin injections, surgical treatment and (f) neuro-urological rehabilitation

Clean intermittent catheterization: For neuro-urological SCI patients who are unable to empty their bladder effectively, clean intermittent self-catheterisation is the gold standard of treatment. Intermittent catheterization involves the placement of a catheter to drain baldder's urine and its immediate removal after completion. This is repeated at regular intervals throughout the day and is performed with either a disposable or a reusable catheter [15,18-19]. Intermittent catheterization is performed by the patient or his caregiver in the rehabilitation center or home environment using a clean technique. According to the latest guidelines, nurses should use their clinical judgment to determine the technique and type of catheter, always according to the needs and particularities of each patient [20]. Sterile intermittent catheterization as originally proposed by Gutmann and Frankel significantly reduces the risk of urinary tract infection and bacteriuria, compared to the clean intermittent catheterization proposed by Lapides et al [21]. However, it has not yet been documented whether the occurrence of urinary tract infections, or patient satisfaction are associated with sterile or clean techniques or by any other factor. The sterile technique cannot be considered a routine procedure. The clean intermittent catheterization technique is an alternative to the sterile technique.

The use of intermittent catheterization, possibly the aseptic technique, is recommended for patients with urinary retention. Reusable catheters are mainly used in developing countries and are considered more risky in terms of hygiene. They have high availability, high sustainability, low cost and little impact on environment [22-23]. On the other hand, single use catheters are safer, more easy to use but are expensive, difficult to be stored and harmful for the environment [22-25]. A study by Welk et al showed that hydrophilic catheters may be cost effective in comparison with uncoated catheters [26].

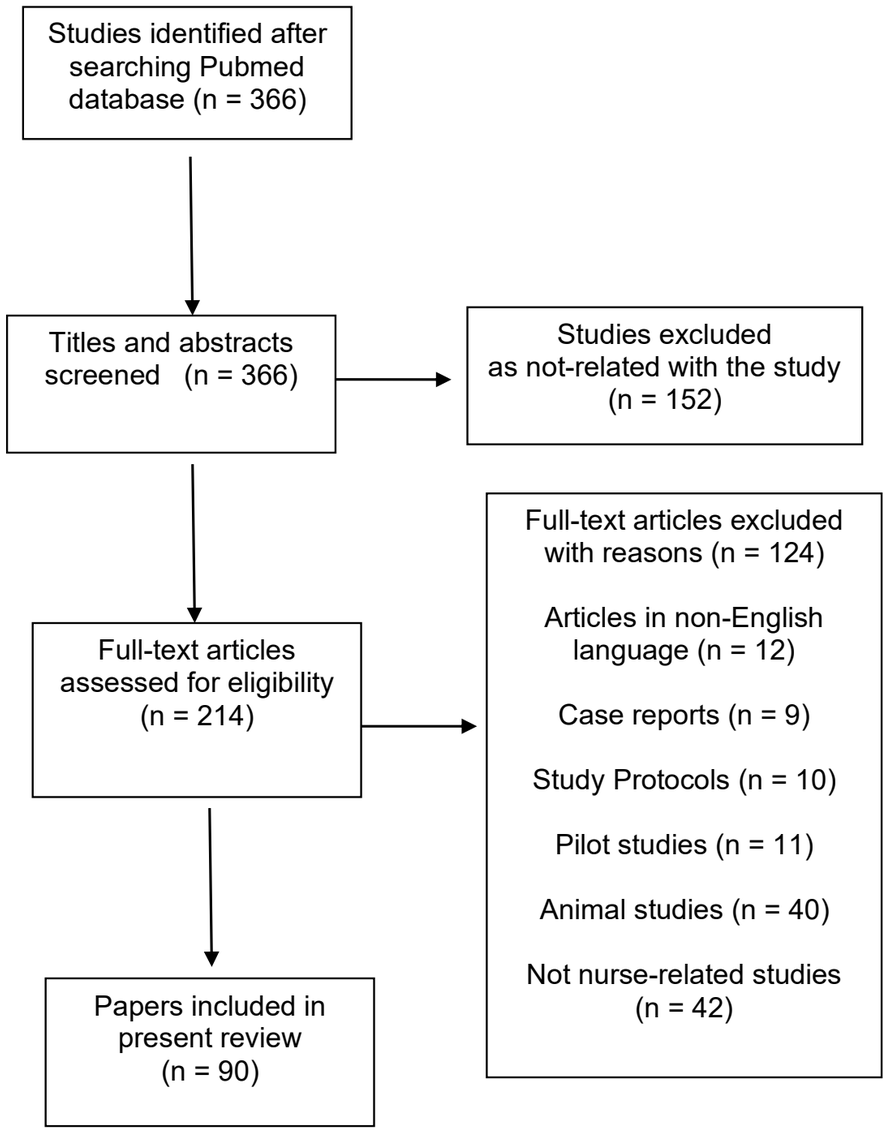
The average frequency of catheterizations per day is 4-6 times and the most commonly used catheter size is between 12-16 Fr. Ideally, the volume of the bladder during catheterization should generally not exceed 400-500ml. The technique can even be applied in SCI patients up to C6-level lesions [12,18,27-30].

Long intervals between catheterizations, makes bladder store excess urine, leading to excessive filling, reduction of bladder blood flow and detrusor myogenic damage, further increasing the risk of reflux. When the intervals are short, frequent catheterizations increases the risk of urinary tract infections and affect the bladder ability to obtain effective systolic and diastolic training [14,29]. Therefore, frequency of catheterizations depends on the residual urine volume and maximum urine output [14,31].

This method of the intermittent catheterization has an advantage over permanent catheterization, as it reduces the frequency of long-term complications, such as hydronephrosis, kidney stone growth and bladder. SCI patients who use intermittent catheterization suffer fewer lower urinary tract symptoms, enjoy better sleep and improve physical activities, resulting in a better quality of life. Sterile technique is used in hospitalized patients, but aseptic technique is widely used in clinical practice [20,27,32-36].

Intermittent catheterization is contraindicated for patients who do not have upper extremity functionality to perform the procedure themselves, patients who do not have someone willing or suitable to help them in this process, when there is poor cognitive function, inability or reluctance to meet the catheterization schedule or fluid intake pattern, and when there is an adverse reaction, from the continuous insertion of the catheter into the genital area [27,37-40]. According to

Figure 1



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Crescenze et al, female gender, earlier injury, recurrent urinary tract infections and severe bowel dysfunction were associated with dissatisfaction for clean intermittent catheterization of SCI patients [41,42].

Indwelling catheters: The use of an indwelling catheter involves inserting a catheter into the bladder for a short or long period of time. The two types of Indwelling catheter are the transurethral catheter and the suprapubic catheter. Permanent transurethral catheterization, and to a lesser extent suprapubic cystostomy are associated with a wide range of complications as well as an increased risk of urinary tract infections [43,44]. SCI patients with indwelling catheters were almost twice as likely to report more severe bowel symptoms as those performing clean intermittent catheterization [45]. In this way, both prior techniques should be avoided whenever possible. Silicone catheters are preferred as they are less prone to sediment deposition and the high probability of latex allergy in neuro-urological patients.

Condom catheter drainage: Social restraint can be achieved by collecting urine with various devices such as incontinence diapers. Condom catheters with a urine collection device are a practical method for men. Patients should be closely monitored for the risk of urinary tract infections. The penile pressure-closure device is completely contraindicated in patients with extrinsic hyperactivity or low-dilation bladder because there is a risk of developing high intravesical pressures and wounding or necrosis due to reduced or absent sensation [15].

Assisted bladder emptying: Bladder emptying without catheters is the top priority for restoring bladder function [46]. Incomplete emptying of the bladder is a serious risk factor for urinary tract infection, development of high intravesical pressure and incontinence. Therefore, various methods can be applied to improve the emptying process. Downward movement of the lower abdomen with suprapubic compression (Credé) or increased intra-abdominal pressure (Valsalva) leads to an increase in intra-cystic pressure, but can usually also cause reflex contraction of the sphincter [10,15]. The latter can increase the outflow resistance of the bladder and lead to inefficient emptying. The high pressures that develop during these procedures are dangerous for the urinary system. Therefore, their application should be discouraged, unless urodynamic testing shows that the intracystic pressure remains within safe limits. Long-term complications are inevitable for both of these emptying methods. Already insufficient pelvic floor function may worsen further, causing or exacerbating pre-existing urinary incontinence [14].

The risk of high pressure urination is real and interventions to reduce peripheral resistance may be necessary. This stimulation can also cause autonomic dysreflexia, especially in patients with high SCI (at or above the T6 level). All assisted bladder emptying techniques require low peripheral (urethral) resistances. Even then, high extruder pressures can develop. Therefore, patients need careful training and close urodynamic and urological monitoring [6].

Gradual training and prevention of urinary tract infections can be performed. Bladder training absorbs much of a patient's time, which can be discouraging. But perseverance is necessary, because the bladder will gradually train. The same training is done for both sexes, but it is absolutely necessary for women, as there is no satisfactory catheter in the market. Incontinence diapers are the only protection in case of leaks between discharges or catheters. When bladder training is ineffective, the patient learns self-catheterization with an intermittent but not always regular schedule [6]. Continuous nursing care intervention can improve patients' compliance and psychological aspects and reduce urinary complications [47-48].

Oral drug therapy, botulinum toxin injections, surgical treatment: A single, optimal, medical treatment for neuro-urological symptoms is not yet available. Usually, a combination of different treatments (eg intermittent catheterization and antimuscarinic drugs) is recommended to prevent urinary tract damage and improve long-term results, especially in patients with suprasacral SCIs [49]. Antimuscarinics are the first line of treatment [12]. The administration of probiotics may be useful for the prevention of urinary tract infections in these patients [50]. Botulinum toxin injections for urinary incontinence are associated with about 50% patients' satisfaction [15,51-53]. Addition of gabapentin can be considered as an alternative, before Botulinum toxin injection, for SCI patients with neurogenic overactive detrusor who did not respond

to the combination of anticholinergics and mirabegron [54]. Augmentation cystoplasty is a well described surgical method aiming to control incontinence risk factors and long-term complications [12,55-57].

Neuro-urological rehabilitation: The term bladder rehabilitation summarizes the treatment options aimed at restoring bladder function in SCI patients with neuro-urological symptoms. Strong contraction of the urethral and / or pelvic floor sphincter, as well as anal dilation, manipulation of the genital area, and physical activity inhibit urination through a reflex arc. Relevant methods include temporary peripheral electric stimulation, peripheral electric stimulation combined with pelvic floor muscles training, intracystic electric stimulation and repeated transcranial magnetic stimulation [14,58-64]. Sacral neuromodulation has shown conflicting results with a favourable outcome ranging from 29% to 40% in the testing phase and 58% to 80% in the permanent phase [1]. Electrical stimulation of the genital nerves (GNS) is a tolerable method that acutely inhibits reflex neurogenic detrusor overactivity and bladder contractions and may increase bladder capacity [65-66].

Principles of Neurogenic Bowel Treatment

Treatment of bowel dysfunction in SCI patients is of vital importance, as it is associated with a negative impact in quality of life [4]. Prevention of fecal incontinence is the top priority for restoring bowel function [46]. Proper bowel care reduces the risk of autonomic dysreflexia [45,67]. Fecal incontinence was associated with urinary incontinence and impaired satisfaction with life [68]. The rate of fecal incontinence increases significantly with increasing age, myelomeningocele as etiology of injury, completeness of SCI, and permanent use of wheelchair [68-69]. Education to nurses, rehabilitation team and patients is important to facilitate a neurogenic bowel program in the acute care trauma setting [5].

The role of the nursing team is significant and proper skills and education are needed [70]. An appropriate and consistent bowel care routine implemented by properly educated nursing team enables SCI patients to experience wellness and quality in their everyday lives [71]. It is proved that nursing intervention contributes to recovery of bowel function and improvement of SCI patients' quality of life and satisfaction [72]. Todd et al observed that, nurses providing bowel care to SCI patients, accepted unpleasantly their duty for bowel care, and often saw it as low priority displaying avoidance tactics. Provision of care in these patients may facilitated by the standardization of bowel care training. More properly educated nurses are needed to improve the level of treatment [73].

In the first management phase of the neurogenic bowel, proper nutrition, satisfactory fluid intake and bowel emptying program are necessary for SCI patients. The training of the SCI patient for the operation of the rectum is necessary to be carried out immediately after the installation of the lesion and regardless of the level of the SCI [74]. According to Attabib et al, in patients with traumatic cauda equina injury, shorter time from injury to initiation of rehabilitation was a significant predictor for bowel function. Patients with traumatic cauda equina injury have a reasonable chance of recovery in bowel and bladder function [75].

For bowel care, the right training program starts as soon as the patient is on a complete diet. The goal is to transfer bowel contents to the rectum and remove it with reflex defecation when the patient is prepared [76]. Proper evaluation and the creation of a personalized program, combined with patient monitoring and education, are important parameters of the process. Individual MR-defecography findings in complete SCI patients may help to determine specific therapeutical options for patients suffering from severe bowel dysfunction [77]. The development of an effective bowel function program may include measures such as [78]: (a) adequate and appropriate intake of food and fluids, (b) use of dietary supplements and oral medications when necessary, (c) selection of appropriate methods to aid defecation and emptying and (d) colostomy surgery.

Adequate and appropriate intake of food and fluids: The Mediterranean diet, combined with exercise and dietary supplements, has been proposed in SCI patients. However, chronic SCI patients consume fruits, vegetables and whole grains in less quantity than the recommended guidelines. This can be explained by the fact that symptoms of bowel dysfunction may be increased after high fiber consumption. Low fiber consumption triggers dysbiosis, which is associated with both endotoxemia and inflammation [79-80]. Approximate daily consumption of 15 gr dietary fibers has been shown to be beneficial in the management of neurogenic bowel in SCI patients [81].

Use of oral medications: Conservative, pharmacological management of neurogenic bowel dysfunction is successful in 67% of the SCI patients [82]. Opioids have a significant constipation effect [83].

Selection of appropriate methods to aid defecation and emptying: Selection of appropriate methods to aid defecation and emptying, such as natural techniques (manual emptying, rectal and anal canal irritation with appropriate body positioning) and defecation stimulants such as suppositories, enemas and laxatives [76,84]. The neurogenic bowel is best treated when the rectum is emptied at a specific time, the same hours that the person maintained and before the injury. Laxatives are administered 6-8 hours before the specified time of rectal emptying. Bowel management typically includes mechanical distension of the distal colon to evoke a recto-colic reflex and induce bowel emptying. The induction of true emptying can be achieved by administering a glycerol suppository, thus stimulating the defecation reflexes, causing gas and chemical irritation of the mucosa [85]. Evacuation takes place either in bed or in the toilet. For most patients, this procedure is done with help [76]. Colonic stimulation may have the potential to improve colonic motility for individuals with neurogenic bowel dysfunction [86]. However, it has been found that 1/3 of the SCI patients has no information about transanal irrigation [87]. Electric stimulation may be beneficial for neurogenic bowel in SCI patients [64,88].

Colostomy surgery: Colostomy surgery to achieve bowel emptying is a safe and effective method when performed early after SCI. Colostomy may help newly injured patients to gain independence and make bowel care easier and more acceptable [89]. Most SCI patients experience improvement in quality of life after colostomy procedures [90].

Other methods: Transdermal administration of neostigmine / glycopyrrolate by iontophoresis has been suggested as an easy, safe, and effective method to promote bowel evacuation in SCI patients [91].

Conclusions

Neurogenic bladder and neurogenic bowel are a major challenge for SCI patients in the long term. Treatment modalities in SCI patients with neurogenic bladder include clean intermittent catheterization, indwelling catheters, bladder function training and assisted bladder emptying. Neurogenic bowel may be treated with adequate and appropriate intake of food and fluids, use of dietary supplements and oral medications, selection of appropriate methods to aid defecation and emptying and colostomy surgery. The role of nursing care is of vital importance as it can prevent further injury and contribute to improvement of patients' quality of life.

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The impact of walking on spinal cord tissue regeneration in patients with paraplegia following spinal cord Injury

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ABSTRACT

The impact of walking in Spinal Cord Injury can promote axonal growth through directed neuroplasticity. The impact of walking in corticospinal tracts, in combination with proprioception, could be the key to neuroregeneration. Furthermore, growth factors such as brain-derived neurotrophic factor (BDNF) and insulin growth factor -1 (IGF-1) play a crucial role not only in the procedure of axonal growth but also in the remyelination.

Many posttraumatic treatment strategies have been evaluated until now, including pharmacological agents aimingto block the development of secondary apoptotic mechanisms of CNS. The same strategies are simultaneously able to promote the regeneration of neuroaxons. Nevertheless, there is insufficient knowledge concerning the hypothesis that gait training could be applied as a potential therapy for neuroprotection following SCI.

The objective of this review is to assess the impact of assisted walking in paraplegia by consolidating evidence regarding: (a) neuroplasticity (b) tissue regeneration.

Key Words: "SCI", "neuroplasticity", "regeneration", "paraplegia", "proprioception", "gait training"

Introduction

According to the International Spinal Cord Society ISCoS, Spinal cord injury (SCI) is a severe neural trauma that, depending on the severity of the damaged segment, is classified into complete and incomplete. Statistically, it is assessed that 0.0022% of the global population will suffer from a spinal cord injury (SCI), annually [1]. Most of the patients with complete SCI are considered as clinically incomplete due to a few remaining neuron connections based on EMG results [2,3].

Paraplegia refers to the impairment and loss of motor, sensory and/or autonomic function in the thoracic, lumbar or sacral segments [4]. It is a result of severe damage to the spinal cord and the nervous system [5,6]. Recovery following SCI is proved to be perplexed and requires long-term rehabilitation [4]. A hallmark of posttraumatic SCI is neuroplasticity, enabling nervous system to modify and change neural networks to adapt both neuronal structure and function [7-10].

The process of tissue regeneration following SCI

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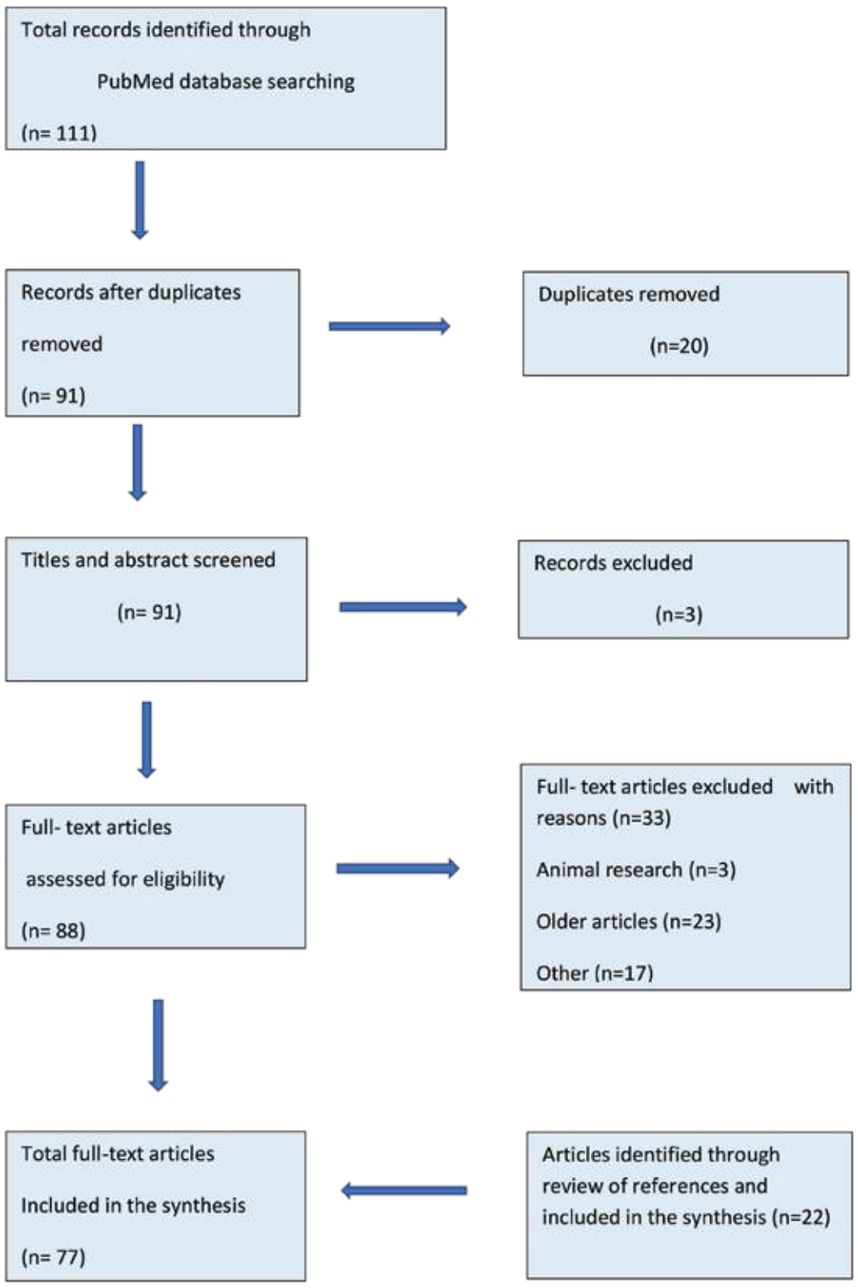

Figure 1: Flowchart of the Article Selection and Review Process

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could be differentiated into two phases, the subacute and the chronic phase [5]. The subacute phase refers to some weeks following injury and the chronic to some months-years post-trauma [9]. Walking has been always a goal of the chronic-phase SCI rehabilitation program, concerning locomotion function [11-13]. Nonetheless, there are questions on how walking can affect neuroplasticity and tissue regeneration. This is a potential oversight to assume walking as a therapy.

The main purpose of this review is to provide proof that locomotion training on the treadmill [61], gait-assisted orthosis such as Locomat and wearable exoskeleton robots are capable to foster spinal cord tissue regeneration and promote neuroplasticity through re-learning gait, in individuals with SCI [10]. Although the existing data about this issue is limited and quite perplexing, especially in human subjects, there are some research articles, meta-analysis and systematic reviews that could prove this hypothesis. Successful and functional nerve tissue regeneration should be supported from supraspinal tracts [62], spinal and peripheral inputs to be long- lasting and functional [63].

Pubmed database was reviewed to identify ways that walking can foster spinal cord tissue regeneration and promote neuroplasticity. The key words "SCI", "neuroplasticity", "regeneration", "paraplegia", "proprioception" and "gait training" were used. Search parameters were specific regarding date of publication (from 1995 until 2022) and relevance. The process of identification and the criteria of inclusion-exclusion are described on the following flowchart (Figure 1).

Discussion

The initial electronic database search resulted in a total of 111 articles, of these, 77 were considered for inclusion in this review (Figure 1).

Pathophysiology of Spinal Cord Injury

SCI consist of two major pathophysiological mechanisms, primary and secondary [5,6,14]. The primary refers to the immediate mechanical traumatic damage of spinal cord, leading to demyelination and axotomy [15-17]. Secondary injury involves the presence of free radicals due to the long ischemia and hypoxia [4-6]. Neurotransmission is impaired, lipid peroxidation and calcium influx contribute to apoptosis and axonal demyelination [4,14-17]. Finally, scar and cavitation are formed, inhibiting myelin regeneration and limiting axon growth [4,5].

Neuroplasticity of Spinal Cord

Based on the metaplasticity theory, morphology and function of a synapse can change over time [9,18]. Following SCI, the following plasticity includes the neural circuit reconstruction, activation of neurons and nerve conduction [8,19]. The regulation of microenvironment and molecularis aim at neuroprotection of intact axons and gene regulation [20,21]. Specifically, neurotrophic factors such as the brain derived nerve factor–BDNF and insulin growth factor-1 (IGF-1) have been proved to promote adaptive spinal plasticity [20,21,28]. As an adaptive spinal plasticity can be referred as task-dependent plasticity which can be succeed by special forms of training such as stepping [11,19,22].

In patients with paraplegia, stepping may be an effective approach to direct and enhance plasticity however the major question is how [25]. Assisted walking can be defined as a direct-task plasticity specific training of motor function [25]. Hence, the improvement of functional ability of individuals with paraplegia can be translated into enhancement in neuroplasticity. The parameters of these indications are gait speed, intensity, and duration of gait training [25,27]. Literature data support that the improvement of intensity and gait speed are proved to be an indicator of increased plasticity [27].

Research conducted by Leech et al investigated that high-intensive treadmill training in patients with incomplete chronic SCI has an important influence on serum concentration of the brain-derived neurotrophic factor BDNF [28]. The authors demonstrated increased levels of peripheral sBDNF after acute intensive gait training of 11 individuals with SCI [28]. Except from sBDNF, the researchers proved that treadmill training can also affect IGF-1 serum concentration levels [28]. Although there was no correlation between speed and intensity and serum levels of IGF-1, treadmill training increased the levels of IGF-1 following exercise in general [28]. Taking into consideration that insulin-growth factor-1 (IGF-1) is involved in synaptic protein synthesis and interacts with BDNF [20,21], this means that neuroregeneration can be promoted also on a molec-

ular level. Neurotrophic factor BDNF promotes adaptive plasticity which is required for the creation of functional neural connections in SCI [28].

From Tissue Regeneration to Functional Synapsis

The scientific issue of neurogenesis and neuroregeneration in neuroscience has not been completely solved [23,24]. Nowadays, there is limited research data on neural repair following SCI and the mechanisms underneath axon restoration and reconstruction [23]. Nevertheless, the function and efficiency of tissue regeneration mechanisms is still under investigation [5]. Anatomically, there are three broad routes to successfully achieving restitution of functional circuitry [6,18]. The one is the regeneration of damaged axons in long distance, the other is sprouting of lesioned neuron and get connected with the intact ones or alternatively sprouting of undamaged axons and properly joined with the cut neuron [6,18]. The three broad routes alone are inadequate for functional synapsis [18]. Hence, there are some presuppositions that contribute to functional restitution [6,76]. The damaged axons must appropriately guide to the right direction, maintain a long-distance axon growth, circumvent the glial scars, develop mechanisms of remyelination and finally form functional synapses with the intact neurons [18,77].

The remyelination of axons after SCI is an overly complex process [15]. Nevertheless, it is generally accepted that the trophic factor BDNF, Schwann cells and oligodendrocyte precursor cells are involved in remyelinating spared axons, thereby contributing to tissue regeneration [15,16,26]. The growth factor BDNF has been proved to promote adaptive spinal plasticity, thus it can be assumed that there is an interaction between the process of neuroplasticity of spinal neurons and myelin production [28,29].Furthermore, Schwann cells are well known as the myelinating cells of peripheral nervous system [29,30]. However, they can gain access to spinal axons and assist in forming myelin [30]. This means that peripheral nervous system can influence in a positive way the damaged spinal circuits as far as myelin regeneration is concerned [15]. Eventually, oligodendrocyte precursor cells (OPCs) which originate both from the subventricular zone (SVZ) and locally, migrate to the SCI lesion site to differentiate into myelin-producing oligodendrocytes [15,31,32].

Axon outgrowth can be sustained only if axonal debris of the damaged neurons can be surpassed. Microglia is the major innate immune cell class in the brain and spinal cord [33]. Using its phagocytosis function, microglia could participate in the maintenance of structural and functional homeostasis of the central nervous system, such as normal myelin turnover and activity-dependent synaptic plasticity [33]. This phagocytosis is significantly up-regulated after injury, as a part of the injury-associated inflammatory responses, to engulf damaged neuronal and axonal debris [33].

Proprioceptive Afferent Promote Neuroplasticity

Proprioceptive feedback incorporated signals from ankle extensors during stance and swing phases of walking [19,34,35]. To begin with, the leg extensor muscles provide load-related afferent information to the spinal cord [36,37]. The activation of these muscles is produced through loading of the sole of the foot during stance phase [37,38]. These activations occur a hip-joint related afferent input, which are appropriate for the initiation of the swing phase [38,39,40]. A study demonstrated that without loading the sole of the foot during the stance phase, no meaningful leg muscle activation occurs in people with complete paraplegia during supporting stepping [41].

Another principal factor that depends on afferent proprioception is the automatism of moving limbs [42]. Spinal automatism is provided during stepping, influencing the coordination of the limbs during locomotion [19,36,42]. In SCI, there is need for training, imitating the automatism and coordination of normal stepping [19,42]. Thus, a basic requirement to induce a locomotion pattern in the thoracolumbar spinal cord can be an assisting training, providing sufficient proprioceptive feedback [36].

Training effects in patients with SCI depend on some number of physiological prerequisites necessary to evoke a pattern of muscle activation like those individuals without SCI to promote adaptive neuroplasticity [19,43,44]. A fundamental factor that is required to trigger a locomotor EMG pattern in SCI patients is an afferent input from load receptors [39,45]. Proprioceptive inflow from leg extensor muscles and mechanoreceptors in the sole of the foot, provide load-related afferent information [19,41]. Hip joint-related afferent inputs also play a major role in the generation of a locomotor EMG pattern, in individuals with incomplete spinal cord injury [19,41].

The activation of load receptors and hip-joint related proprioceptive receptors (hip extension) lead to a physiological leg muscle activity pattern during stepping [38]. The research proved that proprioceptive input produced during assisted walking led to targeted leg muscle activation. Electromyographic activity (EMG) of patients with SCI showed great improvement and similarities to normal walking [34,40,46].

Locomotion Rehabilitation Influence Plasticity and Regeneration

It appears that, through gait training, the spinal cord acquires the ability to respond to the imposed patterns of sensory inputs [47,48]. The aim is to retrain the nervous system, stimulating a form of learning that regenerates the surviving circuits and promotes new neuronal connections [22,48]. Stepping, as a spinal learning process, can strengthen the efficacy of neural pathways [47].

Neural excitability within the spinal cord is regulated by motoneurons / interneurons [49]. Khan et al demonstrated that intensive walking training counterpoise the abnormal H-reflex, clonus and stretch reflex following SCI [41,49-52]. Furthermore, the increased impact of corticospinal inputs to interneurons [53] due to training strengthened the inhibitory control of spinal circuits [49]. Additional research demonstrated that gait-assisted training generated and modulated soleus H-reflex [54,66]. Consequently, gait training strengthens spinal descending control and promotes adaptive plasticity [50,51,52].

Cortical and spinal excitability must be increased to activate pyramidal axons and interneurons including spinal intrinsic networks [65,67]. Thomas et al., examine the impact of intensive treadmill training on human spared corticospinal pathways directly [68] and not only based on walking function parameters [11,13]. The authors evaluated patients with chronic SCI and demonstrated that corticospinal tract function was enhanced after intensive daily treadmill training for several months [68]. The researchers used the system of TMS-evoked MEPs to measure corticospinal excitability, which was quite increased after training. Moreover, the patients were examined again after 2,5 years, and the results were maintained [68]. Therefore, the results of motor evoked potentials (MEP) might be an indication of nerve sprouting on spinal level [57,64].

Spared corticospinal tract (CST)[65] and proprioceptive afferent (PA) axons are both able to sprout after injury and contribute to rewiring spinal circuits, affecting motor recovery [70]. Proprioceptive afferents and descending motor pathways, including the CST, are the two major classes of extrinsic inputs to spinal segmental motor circuits [70,71]. They closely interact with each other during postural control, locomotion, and voluntary movements [70-72]. Both ipsilateral CST and PA axons are very sparse in lamina V to VII of spinal cord and there is minimal overlap between them [70-72]. Taking this fact for granted, it can be a parallel sprouting of proprioceptive afferents and CST axons [27].

Robot- assisted gait training in Paraplegia

Robot-assisted gait training (RAGT) is separated into two categories: the grounded exoskeleton robots (Locomat) [22,34,55] and the wearable exoskeleton robots [76] such as ReWalk [56], Ekso, REX, Indego, and HAL [13,57]. FDA or CE officially approves all [22]. The major difference of these two robot systems is that Locomat is a stationary walking system including a grounded exoskeleton based on a treadmill, whereas the wearable exoskeleton utilizes various environments for gait training [22]. The main purpose of the two exoskeleton robots is to support SCI patients' bodyweight to re-educate walking [58]. Studies proved that RAGT improve neuromuscular relearning in patients with SCI [55,59,60].

Important research with 11 incomplete patients with paraplegia provided supportive evidence for the clinical potential of gait–assisted training with an exoskeleton. Particularly, all participants were trained with the assistance of BWSTT with HAL exoskeleton for 12 weeks [57]. The authors reported that plastic changes appeared in sensorimotor cortical region (S1) after training and long ago after it [57]. Nevertheless, more research is required in this field.

A case study with four patients with tetraplegia evaluated brain plasticity after training with body weight-supported treadmill (BWSTT) and Locomat orthosis [69]. Evidence of great significance was found by the investigators, who demonstrated supraspinal plasticity after 12-week training [69]. The assessment was made with fMRI imaging, proving an increased activation of sensorimotor cortical region (S1,S2) [12,69]. Furthermore, for the participants who achieved functional improvement in over-ground locomotion, the fMRI depicted an enhanced activation of cerebellum [69]. Therefore, it can be assumed that these results may be a consequence of axonal regeneration on spinal level. Consequently, further research should be performed to investigate whether spinal tissue regeneration can be associated with previous results.

Limitations

One limitation of this study is that there was limited exclusive data available on paraplegic patients, since most of research papers also include quadriplegics due to the difficulty of finding subjects for research. Another restriction was the diversity of evaluating techniques used in the studies. For instance, some researchers use fMRI depiction and others measure the concentration of molecules in serum levels.

Conclusion

This review is the first to refer to locomotion rehabilitation as a method to promote nerve tissue regeneration. There are many presuppositions for a successful sprouting and nerve connection. The overall approach of supraspinal, spinal and peripheral tracts can be the key to directed plasticity.

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Sciwora: Diagnosis and treatment A systematic review

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ABSTRACT

SCIWORA (Spinal Cord Injury Without overt Radiological Abnormality) is a term first used by Loyd, back in 1907, even though it became more known in 1982 by Pang. The initial term described a condition were signs of myelopathy were not accompanied by traumatic findings on plain radiographs or on computed tomography and it was mostly believed to be a medical condition seen in children. Throughout the years it has been shown that SCIWORA is not only seen in children but it is also seen in adults. Introducing MRI to the diagnostic algorithm caused controversy about what should be defined as SCIWORA, but it also added to the comprehension of the pathophysiology of SCIWORA. The aim of this study was to investigate the current trends in diagnosis and possible treatments of SCIWORA. The reviewed articles were obtained by using the online Pubmed and Google scholar databases and by following the PRISMA guidelines. While there is no consensus on a protocol, the current management protocols include immediate bracing, avoiding the administration of corticosteroids and performing an MRI as the main diagnostic imaging. The decision for surgical intervention seems to be taken based on the MRI findings and the skills of the practitioner.

Key Words: Sciwora, Sciworet

Introduction

SCIWORA stands for spinal cord injury without overt radiologic abnormality. Pang defined it as a spinal cord injury leading to myelopathy without any findings on radiographs or on computed tomography. 1 At first it was believed to be more frequent in children but through the years it has been found that specific adult groups are also predisposed to SCIWORA. [1, 2, 3, 4]

The symptoms consist of transient numbness to even quadriplegia.[5] Most of times symptoms appear as soon as the injury occurs but cases of late onset SCIWORA have also been reported in the literature.[6,7]

In the past decades, plain radiography and computed tomography had been the main diagnostic tools for spinal cord injuries. Currently MRI is the gold standard in the imaging of these injuries since it evaluates not only the bony structures but also the soft tissue structures as the ligaments, the discs and the spinal cord. [8] It has been stated that the degree of the damage at the soft tissue is proportional to the severity of SCIWORA.[9]

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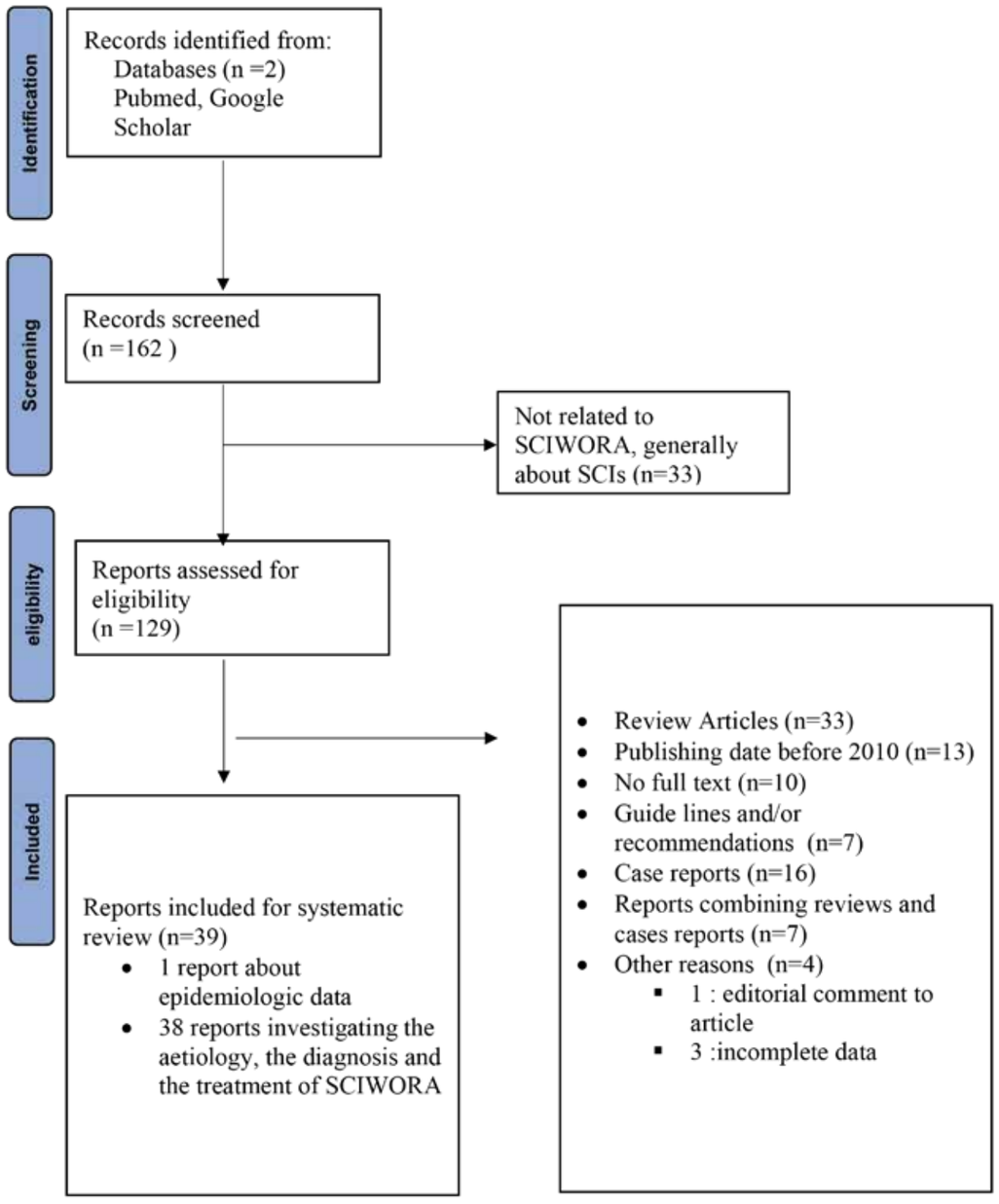

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Even though there are no official guidelines for SCIWORA, the majority of practitioners seem to agree on immediate immobilization of the cervical spine.[10,11,12,13] Administration of corticosteroids (NASCIS protocols) has been debated and even rejected by some.[9,] Surgical treatment has also been discussed as a possibility in patients with deteriorating neurological status[22].

The purpose of this study was to investigate the current diagnostic and treatment protocols of SCIWORA and provide the bigger picture on its controversy. For this reason, a review of the current literature was conducted by using the online Pubmed and Google Scholar databases and following the PRISMA guidelines. Article titles were searched by using the following keywords: "SCIWORA" and "SCIWORET". Studies published after 2010, retrospective studies, prospective studies and clinical studies on surgical treatment were included in the review. On the contrary, studies published in other than English language, review articles, case reports, studies published before 2010, guidelines and/or recommendations, articles combining a review and a case report and articles about spinal cord injuries in general were excluded from this review. Primary search results included 162 articles. After screening of titles and abstracts, 33 articles were excluded since they were generally about Spinal Cord Injuries and not related to SCIWORA, leaving 129 articles for screening. From the remaining 129 studies, 90 were rejected for various reasons (Table 1). Finally, 43 studies were included in this review.

Discussion

SCIWORA is defined as spinal cord injury without overt radiological abnormality. The definition's original description included negative plain radiographs and/or computed tomography.[6] Throughout the years magnetic resonance imaging became an integral diagnostic tool for spinal cord injuries helping at understanding the pathophysiology of the injury but also causing a controversy on which cases should be really diagnosed as SCIWORA.[1,2,2,5,3] Since MRI has been established as the basic imaging method for diagnosing SCIWORA, a number of new terms have been suggested such as SCIWOCTET (Spinal Cord Injury Without Computed Tomography Evidence of Trauma)[15,24], ASCIWORA (Adult SCIWORA)[16,4], SCIWORET (Spinal Cord Injury Without Radiographic Evidence of Trauma)[13,17] , Real SCIWORA[5] and SCIWONA (Spinal Cord Injury Without Neurological Abnormality) [6].

1. **Etiology**

SCIWORA is a traumatic condition of the spinal cord where there is no compromise of the bony structures of the spine. There is no evidence of fractures or subluxations on radiographs and/or computed tomography. SCIWORA's etiology seems to differentiate according to patients' age group. [1,3,7] As a matter of fact, patients with SCIWORA can be divided in two age groups, children and infants younger than 8 years old and adults older than 60 years old .[1]

Children are anatomically predisposed to SCIWORA due to a series of reasons. Firstly the size of their head is relatively larger and heavier comparatively to the size of the adult head resulting in movements that shift the maximum force to the C2-C3 spinal level.[8] Furthermore, it has been shown that the pediatric spine is quite elastic in contrast with the spinal cord: the spine can be stretched by 2'' while the cord can only be stretched by 0.25'' before it shows signs of trauma.[9] This is due to the horizontal and shallow facet joints, the stretchable ligaments and the fact that the uncinated processes are still absent[22]. This is also supported by cadaver studies which revealed that flexion injuries to the pediatric spine were capable of causing subluxation resulting to myelopathy, but no damage at the bony and ligamentous structures.[26] Makino et al, reviewed postmortem multidetector computer tomography scans (MDCT) which were performed within the forensic investigations. Before the autopsy, an MDCT was performed and the scans were interpreted by radiologists experienced in forensic radiology. The study came to the conclusion that MDCT is not capable of replacing autopsy for diagnosing SCIWORA. In addition, children younger than 8 years old have delicate blood vessels supplying the spinal cord, making them even more prone to such injuries[22].

Adults older than 60 constitute the second high risk group for suffering SCIWORA. [1] Adult patients diagnosed with SCIWORA have been reported to have a number of anatomic changes on their spine. The re-

duced diameter of the cervical spinal canal [10] and the degenerative changes of the spine that are expected in this age group[11,3] are the main aggravating factors. Additionally MRI proved that 76% of patients with SCIWORA had herniated discs. [10,15] Makino's study confirmed the existence of disc herniations and disc injuries in these patients.[12]

2. Mechanism of injury

A number of different types of injuries can cause SCIWORA,and the most common are motor vehicle accidents and falls.[13,20]. Falls from heights is the next most common cause. Less often, sports related injuries can cause SCIWORA. Not so common causes include being stricken by a moving object, penetrating injuries and assaults. [14]

Regardless of the cause of injury, the underlying mechanism of injury is usually hyperextension movement of the neck.[5] The exact way that hyperextension causes SCIWORA is still being analyzed but it is suggested that hyperextension leads to a temporary occlusion of the vertebral arteries which is followed by a spontaneous return of the vertebrae to their original position, resulting to ischemia.[5] Neonates are highly predisposed to this kind of injury due to the peculiarities of the anatomy of their atlanto-occipital articulation. Hyperextension can also force the interlaminar ligaments forward into the spinal canal, narrowing it down by even half of its diameter.[7] Apart from hyperextension, mechanisms of injury also include flexion, distraction and ischemia. Distraction injuries are mostly seen in children especially younger than 5 years of age.

3. Symptoms of SCIWORA

As it is described, SCIWORA is a traumatic condition leading myelopathy where imaging gives little to no information. The starting point of the diagnostic algorithm is the clinical presentation. Sciwora has a large range of symptoms which may vary from a transitional numbness to a complete quadriplegia. Neurological deficits as hand and arm numbness,[6,15] weakness of the lower extremities, inability to move[33] and even complete paraplegia has been reported.[7] The neurological deficits may be transient or permanent. Transient symptoms seem to resolve within 72 hours. [18] Some researchers have tried to classify the neurological status into categories according to the motor and sensory findings[8]. Diagnosis of SCIWORA in very young children may be challenging because the involuntary reflex movements of the lower limbs mimic the normal movements.[22] In case of upper thoracic injuries the red flag symptoms may be pulmonary complications because of the impaired function of respiratory muscles. [22]Other symptoms that have been reported are neck pain or tenderness, altered mental status and torticollis.[23]

The onset of the symptoms may also differ. Some patients have stated that they only experienced the symptoms at the exact moment of the injury.[5] It has been shown that the time period between the injury and the appearance of the symptoms can range from 30 minutes to even 4 days.[7,29] This delayed onset of symptoms seems to have no obvious correlation with the mechanism of injury or with the age of the patient. [29] This phenomenon is called late onset SCIWORA. Some of the patients who were diagnosed as late onset SCIWORA cases reported that they actually had some transient neurological symptoms at the time of the injury, such as lightning sensation, numbness or paresthesia.5 There was no incident of a second trauma between the time of injury and the final development of the symptoms.[29]However, it is not to be missed that some of the patients who were deemed late onset SCIWORA cases might had symptoms at the time of the injury which were missed in the initial examination.[7]

Recurrent SCIWORA is another phenomenon described in the literature. It is described as a second injury to the spinal cord after the initial injury in the following 3 days to 10 weeks [6]. It is believed that the post traumatic period is a vulnerable period for the spine and according to the reported cases, the second injury is always more severe than the first one.[6,7]

4. Diagnosis of SCIWORA

Diagnosing SCIWORA begins with the arrival of the patient at the emergency room, containing a carefully taken history and clinical evaluation.[6] The majority of the clinical practitioners use the ASIA score to categorize the patient's status according to the neurological deficits.[16] The imaging evaluation used to consist of radiographs of the cervical spine and even an open mouth view of the odontoid.[6] It is obvious that in the era of using only plain radiographs the diagnosis of SCIWORA was done by exclusion. A number of practitioners have discussed the use of dynamic radiographs. Plain radiographs performed with the cervical spine in flexion and extension can indicate the stability of the spine.[31] The timing of their performance has also been discussed as in the acute period of the injury the muscle spasm can change the results, concluding to performing the dynamic radiographs around a week after the injury. [6, 36] However it is not a common tactic anymore as researchers have concluded that the existing instability can cause even more damage to the already injured spinal cord.[17,36] Computed tomography has been used in order to exclude fractures and dislocations as it is the most precise examination when it comes to diagnosing bony abnormalities.[5] MDCT has even been suggested to be part of the investigation of traumatic deaths as it has been shown that there is an interesting correlation between post mortem results and autopsy findings.[28]

In the 80s, somatosensory evoked potentials (SSEPs) were performed usually within 24 hours of patient's admission.[6] However it was soon considered to be a special test rather than a routine test for diagnosing SCIWORA.[7] SSEPs' possible uses could be the detection of subtle posterior column dysfunction, evaluating patients who are comatose or head injured and it could also provide a baseline MRI examination for comparison.[12]

MRI was definitely a breakthrough for diagnosing SCIWORA as it can show the actual damage of the spinal cord when plain radiographs and sometimes even CTs seem normal.[18] In the literature, it is stated that occult instability in SCIWORA was not proven until MRI was added on the tests that were performed on patients.[7] MRI is argued to be the only imaging option when it comes to imaging the damages of the spinal cord.[23] MRI abnormalities can be categorized as extra neural and neural.[1,7] Extra neural abnormalities consist of soft tissue damage as disc herniation, intradiscal hemorrhages and ligamentous damages. [7] On the other hand, neural abnormalities shown on MRI contain disruption of the spinal cord, cord hemorrhage and edema.[7] MRI can also be prognostic of the outcome.[17,25] Most practitioners agree that MRI findings in SCIs can be classified to four patterns; normal MRI, single level edema, multilevel edema and a mix of hemorrhage and edema.[20] Following that, attempts were made to find a correlation between the MRI findings and the clinical presentation in order for MRI to be prognostic and not only diagnostic.[33,12] However MRI is not diagnostic in all cases since it has been documented that patients with persistent neurologic deficits may present with normal MRI.[5] The timing of performing the MRI seems to be related with the findings as it has been shown that sometimes early performed MRIs do not always correlate with the neurological outcome.[8] According to some authors, the best time for performing an MRI is 24-72 hours after the injury.[9] The initial MRI can sometimes show no abnormalities so it has been suggested to perform another MRI in the following 24 and 72 hours.[8] A study by Ouchida et al, compared the MRI results performed within 48 hours and two weeks after the injury. The practitioners concluded that the delayed MRI reflected the severity of the neurological deficits much more precisely than the acutely performed MRI.The MRI performed right after the injury could not show the increased signal intensity or the prevertebral hyper-intensity as they really were.[19] A quite controversial subject is the advanced MRI sequences such as the SWI and the DTI. These are more accurate on imaging hemorrhage but unfortunately they are very sensitive to breathing motion and to artifacts caused by bones.[20] Specifically, DWI has been suggested as an imaging way to evaluate the integrity of white matter tracts in spinal cord due to its ability to depict the microscopic motion of water protons. In summary DWI could be used in order to evaluate the severity of the injury.[20] A few years back, Zhang and Xia suggested that during the surgical intervention of corpectomy and fusion discs that are suspicious for injuring the cord could be injected with iohexol, under C-arm monitoring, in order to check the integrity of the disc. The patients enrolled in the study suffered neurological deficits such as weakness and numbness in their upper and lower limbs. The MRI findings consisted of swollen soft tissue and disc degeneration. The patients underwent anterior cervical surgery. During the surgery the suspected discs were injected. As a result the leakage revealed the degenerated discs. These discs would be removed

and replaced with a cage filled with bone graft.[21]

5. Treatment

There is no universal consensus about the treatment options of SCIWORA. There is an ongoing controversy about whether and when to operate, while the administration of corticosteroids is most likely to be abandoned by the majority of the practitioners.

The treatment of SCIWORA and every spinal cord injury in general begins at the sight of the accident with the placement of a hard collar. Immediate immobilization with a hard collar is the common tactic as well as the use of a fracture board if the thoracic spine is compromised too.[6] The immobilization is continued throughout the management of the patient at the emergency room. In fact, it is stated that the collar should only be removed once the patient is sedated and intubated and the immobilization is then accomplished with sand bags keeping the neck in a neutral position.[34]

The period of immobilization and whether the treatment should remain conservative are the main reasons for debate. Before 1985 a Philadelphia collar was placed for 8 weeks and after it was removed the stability of the spine was checked by dynamic radiographs.[6] After 1985 a Guildford brace was worn for 12 weeks. Additionally, sports were strictly prohibited for 3 months.7 Others suggest avoiding high risk activities for months in order to decrease the possibility of a new injury.[5] Another suggestions was immobilization by halter traction and minimal weight for 3 weeks.2

Along with immobilization, the administration of corticosteroids is being discussed extensively. Practitioners seem to be divided in those who have rejected the NASCIS protocols and those who still administrate corticosteroids combined or not with surgical intervention.[1] It is stated that corticosteroids should be administrated to patients with persistent neurologic deficits.[36] Administrating corticosteroids can lead to a number of complications such as infections of the pulmonary system and gastrointestinal bleeding. However, if administrated in the right dosage, corticosteroids can provide an improvement. This applies in cases that the patient needs to be transferred to another medical unit before a possible surgical intervention.

Recently, it has been suggested that stem cell therapy could be effective in pseudo complete SCIWORA injuries.[22] This means that patients who have axons that are non-functional but they still react to stimulus can benefit from both stem cell therapy and supportive cell therapy. Regeneration of the axons could be supported by the transplantation of neurotrophic factors. These have an anti inflammatory effect over the axons and additionally promote their regeneration.

The decision for surgical intervention in SCIWORA cases is not an easy decision to make since the level of instability is not always obvious. Furthermore surgical intervention always comes with all the possible complications of surgery, including the second hit syndrome. There is no guideline in the literature for when to operate and when to remain conservative so the decision is upon the physician. It seems that pediatric patients have a good outcome with conservative treatment while adult patients usually respond better to surgical intervention, probably due to the increased disc injury and the bulging of the ligamentum flavum.[13]

Researchers have categorized the SCIWORA injuries in four types. Type I means that there is no detectable MRI findings, type IIa means that there are intraneural abnormalities, type IIb means that there are extra neural abnormalities and type IIc means that are both intraneural and extra neural abnormalities are idetified. Some researchers decide whether to operate or not according to what type of SCIWORA the patient suffers from. Type IIc which combines both intraneural and extra neural abnormalities is usually treated surgically.[28] In general, surgery is indicated for unstable injuries, dislocations, progressive deformities and for cases where decompression is needed.

A quite commonly followed operative treatment is expansive laminoplasty which can be combined with fusion if the spine is kyphotic or has degenerative spondylolisthesis.[35] Mazaki et al, studied the neurological status as well as the complications of patients, of which some were treated conservatively and some were operated.[14] The pratitioners concluded that the group of patients that underwent laminoplasty did not show any significant improvement in paralysis. However, the operated group seemed to have high rates of complications, especially of the urinary and respiratory system. Another operative option is anterior discectomy with

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interbody fusion using a cervical cage.[23] This surgical option is described as a common technique in spinal cord injuries but it is only recently applied on SCIWORA cases. This procedure begins with an anterior approach, a discectomy and decompression followed by the positioning of the cervical cage which is usually filled with cancellous autograft. In Huang's study, the outcome was rather positive, improving by one level on the Frankel scale and encountering no postoperative complications.[37] Alongside with laminectomy a durotomy and duroplasty has also been described in the literature.16 According to Zhu's study, durotomy can contribute to the decompression of the spinal cord and improve the neurological status as a result. As he describes, the patients underwent posterior laminectomy and durotomy. The extent of the durotomy was decided upon the segment with edema. The procedure included removal of the hematoma, rinsing with saline and finally suturing the dura. The results of the follow up were rather positive as the practitioners reported that even some patients with spinal cord hemorrhage or contusion marked improvement after surgery. This could mean that early decompression plays some role on the neurological improvement.

Another critical question to be answered is when to operate. The timing of the operation is very important for the neurological outcome. A recent study came to the conclusion that the optimal timing of operation is 3 to 7 days after the injury.[24]

Apart from the surgical procedures that aim to immediate decompress the cord there are also other procedures that are done afterwards in order to correct deformities. It is known that pediatric patients that suffer from SCIWORA develop neuromuscular scoliosis. These long scoliotic curves that are sometimes combined with pelvic obliquity should be treated to improve pelvic balance and hip containment.[25] The followed technique is using pedicle screws.

6. Prognosis

It has been stated that the initial neurologic status is probably the most important prognostic factor. [32] This means that MRI can provide prognostic information according to the signal changes and the area of extension.[1] With further investigation, it has been shown that age over 45 years, the presence of degenerative changes of the spine and severe initial neurological deficit, are factors that contribute to poor outcome. [1] On the other hand, cord edema and age under 45 years seem to be connected with better prognosis.[13] Additionally, the time of surgical treatment is connected to the outcome as it has been shown that the most ideal time to operate is 3-7 days after the injury.[38]

Conclusion

SCIWORA is a rather controversial injury. Throughout the years, researchers have proposed a series of other possible acronyms to be more precise with the diagnosis and findings of SCIWORA. There is not yet a consensus for the treatment, although there have been some studies supporting surgical treatment against conservative. The administration of corticosteroids tends to be abandoned by most practitioners even though some still use them on specific cases. Due to the rarity of the condition there are still many questions that need to be answered in order to have the best possible outcome for patients diagnosed with SCIWORA.

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