MSD Nov.. 2021, Vol 8, No 11

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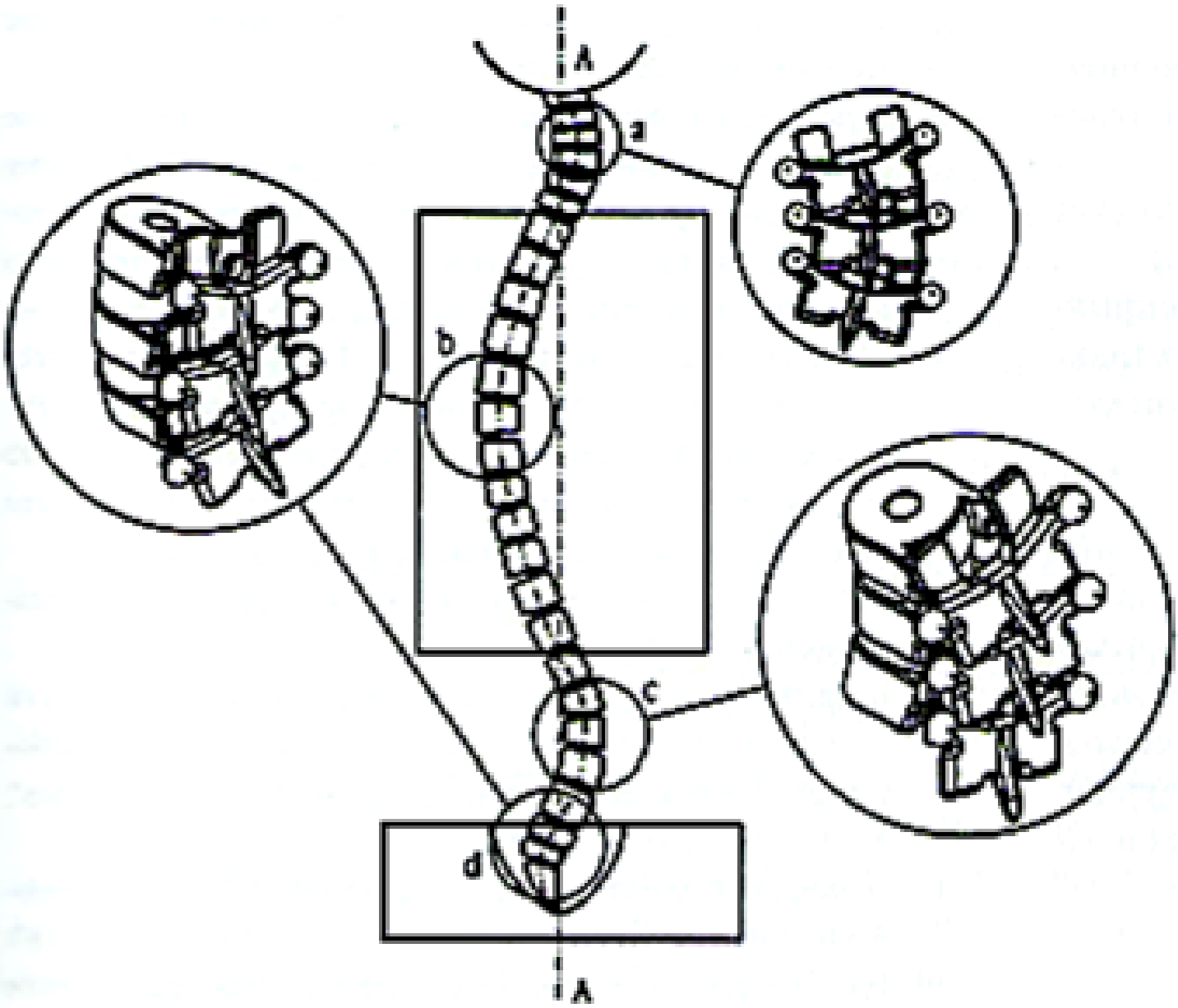

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ISSN: 2148-6832 (Print) E-ISSN: 2148-6832 (Online)

Category: Multi Disciplinary Health Science Journal

Abbreviated key title: Med. Sci. Discov.

Frequency: Monthly

Review System: Double Blind Peer Review

Circulation: Globally, Online, Printed

Article Processing Charge (APC): Free

Licensing: CC-BY-NC 4.0 International License Environmental

Editor-in-Chief: Assoc. Prof. Dr. Dr. Ahmad Rajabzadeh, Anatomical Department of lorestan, University of Medical Sciences, Tabriz, Iran

Established: 30.04.2014

Web address: www.medscidiscovery.com

E-mail : editor [at] medscidiscovery.com

Phone : +44 020 3289 9294

Design and preparation of PDFs, Language editing, Web site design, Graphical design Services of international Journal of Medical Science and Discovery has been contracted with Lycia Press LONDON, UK (as Publisher), by the MSD Board of Directors

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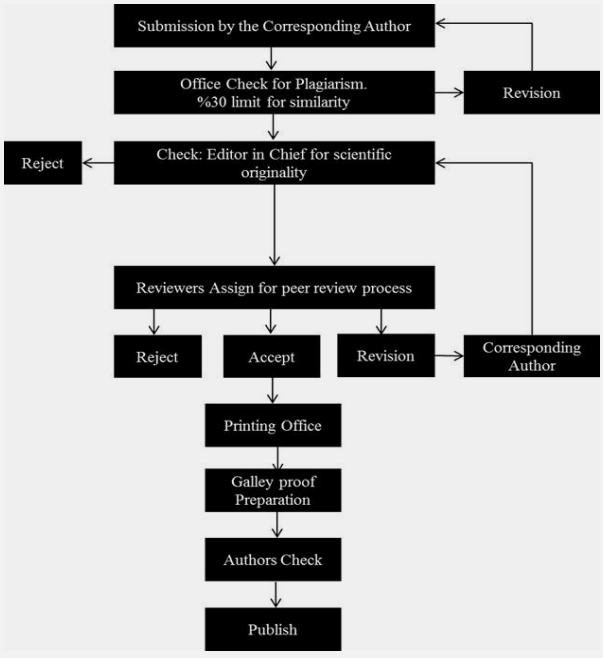

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Medical Science and Discovery
ISSN: 2148-6832

Idiopathic scoliosis. Mechanisms of development

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ABSTRACT

Objective: One of the most complicated problems of Orthopaedics is the treatment of scoliosis. More than 90% of cases are attributable to Idiopathic deformation, the cause of which is unknown. We investigated the cause of pathogenesis of this disorder.

Methods: At our institution more than 6900 patients aged 1-89 years have undergone inpatient and outpatient treatment in connection with spinal pain syndrome and different neurological disorders associated with idiopathic scoliosis. This study was undertaken between February 1996 and February 2010. All patients had a clinical, radiography and laboratory examinations.

Results: The 29.6% of patients were aged 31-50 years old. 60% were men and 40% were women. While examining patients with scoliosis deformation, we noted symptoms of body asymmetry i.e. different volumes of the right and left halves of face body and limbs. These features were typical for all patients irrespective of sex, age, and ethnic origin. 83,2% of patients had underdevelopment of the left part of the body, and only 16,8% of the right side. Analysis of published work in anatomy, physiology, neurophysiology, vertebrology, done simultaneously with analysis of the clinical material, allowed us to make some conclusions.

Conclusions: First asymmetrical structure of the human body is based on laws of nature and is linked with difference of sizes of brain's hemispheres, particularly of the right and left gyrus centralis anterior which controls the muscle's function and our movements. Second asymmetrical tension of Erector spinae muscles, leads to inclination of the pelvis on a side of weak muscles; thus initiating development of the lateral spine curves. Since such a situation is typical for all people, this deformation is known as functional scoliosis. Third, further development of the bodies of vertebrae, their arches, processes, intervertebral discs, ligaments, and other anatomical elements in position of the deviation leads to one sided underdevelopment of these structures. As a result the areas of instability appear in each segment of spine (neck, chest, lumbar and sacral areas).Fourth, the muscles in a growing body misbalance and on the ground of rotating movement, start rotatory dislocation of vertebrae in zones of instability in all parts of the spine. As a result torsion of the deformed wedge-shaped vertebrae leads to formation of the structural scoliosis. The rotation of the vertebrae, described above, does not depend on sex, age and ethnic origin of the patient and has a character of the natural development. Thus from our point of view, the term idiopathic scoliosis, must be changed to spinal muscle asymmetrical deformation of a reflex origin. Understanding of this rotation allowed us to establish an effective non-surgical method of treatment of scoliosis and spinal pain syndrome in patients of all ages.

Key words: scoliosis, idiopathic

INTRODUCTION

Treatment of scoliosis remains a great challenge of orthopedics and has a long history. Physicians of antiquity were concerned with this problem – Pythagoras, Hippocrates and Claudius Galen; the latter have proposed the terms scoliosis, kyphosis and lordosis. Since then, centuries have passed, but the significance of the issue has remained unchanged. Earlier studies of foreign and local investigators were aimed at discovering the ethology of scoliosis. These studies have established that idiopathic scoliosis (IS) or lateral curvature of the spine of unknown ethology is the most frequent among various spinal deformities

Research Article

Received 09-11-2021

Accepted 18-11-2021

Available Online: 22-11-2021

Published 30-11-2021

http://dx.doi.org/10.36472/msd.v8i11.627

(rachitic, cicatricial, paralytic, reflex-painful, discogenic, endocrine, hysterical, emphysematous, hereditary, post-traumatic and others) and constitutes more than 90% of lateral deformities of the spine.

Based on our own significant clinical material, we have set ourselves the goal to reveal the etiopathogenesis of this disease.

MATERIAL and METHODS

From February 1996 till February 2010, we have observed and managed more than 6900 patients aged 1-89 years. These patients suffered from spinal pain, various somatic and neurologic impairments associated with idiopathic deformities of the spine and were managed in the outpatient setting. The majority of patients were 31-50 years of age; 60% were female, 40% - male.

While examining patients with scoliotic deformity, we have always observed signs of asymmetry of the body – different sizes and volumes of the halves of the face, trunk and extremities. These signs were typical for all the patients independent of sex, age and race. Among our patients, we observed underdevelopment of the left side of the body in 83.12% of cases and only in 16.88% - of the right side.

All patients underwent clinical, radiological and laboratory assessments and other tests, if required.

RESULTS and DISCUSSION

Despite numerous scientific papers and publications on the etiology of idiopathic scoliosis the findings were not of a general nature. Since all the studies, including our own, either directly or indirectly were based on the study of the nature of the asymmetry of the body, we decided to arrange the questions in a certain order:

1. What causes the development of the asymmetry of the body?
2. How the lateral curvature of the spine is forming?
3. What comes first – lateral curvature or muscle asymmetry?
4. What are their interrelations?

In search of answers to these questions, we have studied works of classics of domestic and foreign orthopedics, as well as works of experts in anatomy and physiology (**1-5, 14**).

We start the presentation of the results of this analysis with neurophysiological issues.

Anatomy and physiology of interhemispheric differences

Since 1968 papers on the results of post mortem examination of multiple preparations of the human brain were published (**1, 2, 13, 14**) and significant anatomical differences between hemispheres were reported. The area of the temporal cortex, which overlaps Wernicke's area (responsible for semantic speech and also known as Planum Temporale), was notably greater in the left hemisphere in approximately 70% of cases (**Fig. 1** and **2**).

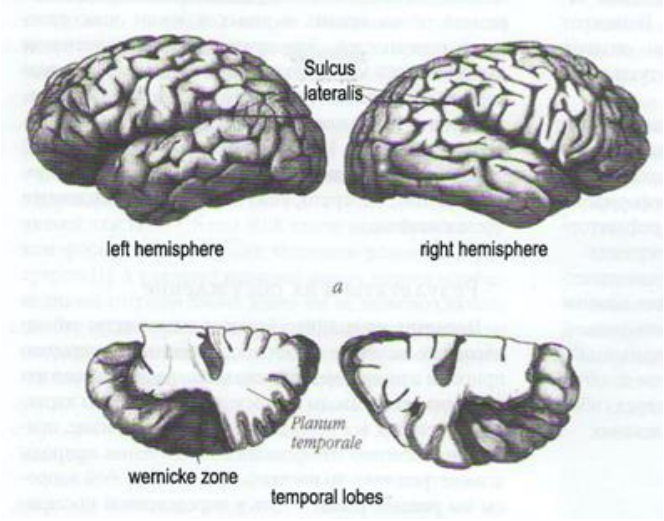

Figure 1. Anatomical asymmetry of cerebral hemispheres. A – Sylvian fissure in the right hemisphere curves upwards at more acute angle; B – posterior part of the Planum Temporale is usually much larger in the left hemisphere, which is associated with verbal functions.

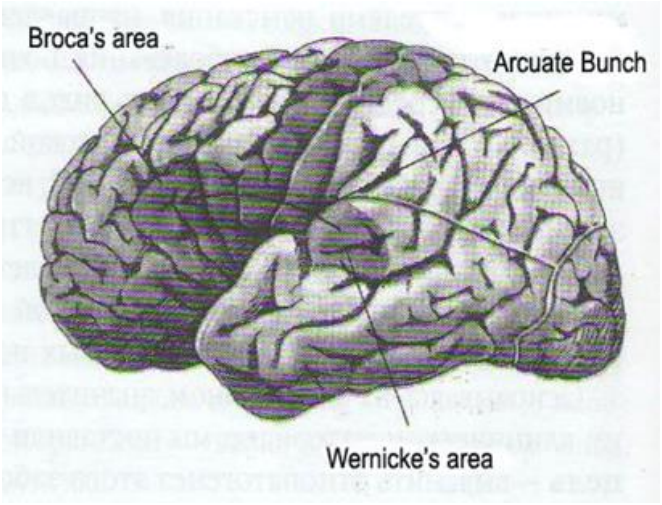

Figure 2. Areas of the left hemisphere involved in speech and its perception. Wernicke's and Broca's areas are interconnected via fibrous tract – so-called fasciculus arcuatum (indicated with the arrow, because this structure is not externally visible).

This asymmetry was also typical for the brain of human fetus. It was demonstrated that Sylvian fissure – a deep sulcus in the cerebral cortex, which separates temporal lobe from the rest of the cortex in the left hemisphere is longer and straighter and is more curved upwards in the right hemisphere. Such asymmetry was also identified in fossil skulls of humans (Neanderthals), which allowed the investigators to suggest that asymmetry of the hemispheres is likely a part of human genetic heritage.

Long-term psychological studies have demonstrated other very important details on brain physiology. Thus, it was shown that in most cases, women are superior to men in verbal skills. These differences are already seen in childhood. Girls begin to talk and read earlier than boys (**1, 13, 14**).

We introduce to the reader another area that deals with the structure and functioning of cerebral hemispheres in the

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prenatal (intrauterine) period. Thus, from the 6th week after fertilization, gonads (sex glands) are formed that initially are the same in both sexes. In male fetus on the 3rd month of intrauterine development gonads start to differentiate to form the testes and secrete male hormone – testosterone under the influence of one or more genes of Y-chromosome. Although testosterone is present in low concentrations in female fetus (certain amount of this hormone is produced in the maternal organism) the level of this hormone in male fetus greatly increases after formation of testes; this inhibits the growth of the left hemisphere and contributes to the development of relatively greater right hemisphere in males (**1, 13, 14**).

- Thereby, we have established the following: left and right cerebral hemispheres are asymmetric, which is predetermined genetically.

Broca's area – a specific zone of the frontal lobe of the left hemisphere that controls all muscles of the face, tongue, jaws and throat. This is achieved through connections of this area with the anterior central gyrus – area of the cerebral cortex that is responsible for motor functions of the right side of the body. Thus, Broca's area can be called motor center for speech.

Wernicke's area – posterior part of the first temporal gyrus, which is responsible for the semantic speech. In 65-70% of cases this area of cerebral cortex is larger in the left hemisphere.

Wernicke's and Broca's areas are interconnected through the arcuate fasciculus that provides synchronous function, i.e. motor and semantic speech constitute a single process.

Given the functional connection of Broca's and Wernicke's areas one can assume that these areas are functioning more active in the left hemisphere than in the right. This causes the muscle tone of the right side of the body to increase in head and neck muscles, as well as in the spine extensors (**Fig. 3**). As a result of their asymmetrical contractility, relative shortening of the lower limb of the weaker side occurs and the trunk tilts to the left. Interestingly, that this hypertonus is also typical for mimic muscles, which may serve as an explanation of facial asymmetry.

In those individuals (11%), in whom Planum Temporale is more developed in the right hemisphere, hypertonus of the spine extensors on the left side causes subsequent tilt of the body to the right. It is what we call a "relative shortening of the right leg" (**Fig. 4**).

High testosterone level during the prenatal period inhibits the growth of the left hemisphere in male fetus compared to females. In boys, such underdevelopment of the left hemisphere and particularly Wernicke's area explains why boys 4 times more frequent than girls are among children who are unable to read, and why girls have more developed verbal skills compared to boys.

If we assume that Broca's and Wernicke's areas in girls are 4 times more active compared to boys, than the latter also have 4-fold increased muscle tone of the spine extensors on the right side. Moreover, considering the fact that the left hemisphere is smaller in boys compared to girls, the difference in muscle tone of the trunk muscles increases even more. Probably, this may explain the universally known fact that lateral (scoliotic) curvature in girls occurs 5-6 times more often than in boys.

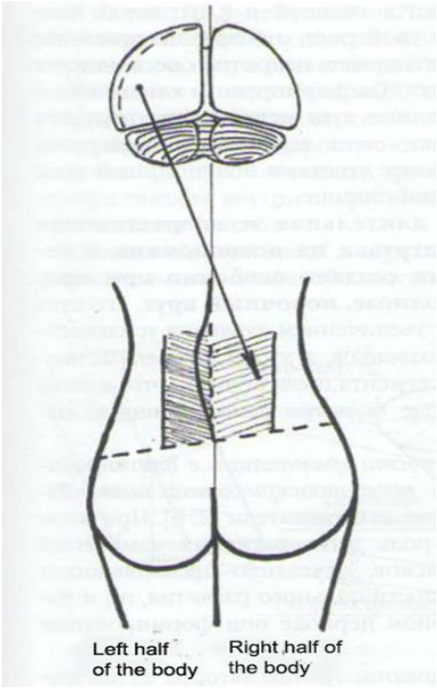

Figure 3. Hyper tonus of spinal extensors on the right is due to increased functional activity of anterior central gyrus of the left hemisphere.

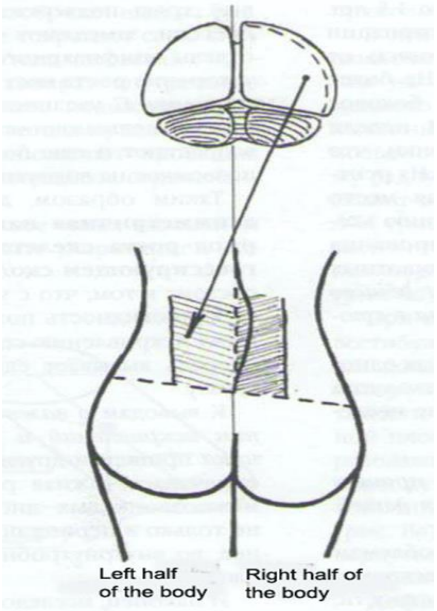

Figure 4. Hypertonus of spinal extensors on the left is due to increased functional activity of anterior central gyrus of the right hemisphere.

As a newborn child gets older, asymmetry of the trunk muscles "fixes" in the cerebellum, which controls all types of movements. Indeed, the cerebellum is often called "the keeper of conditioned reflexes". Months will pass from standing, first and subsequent steps to a stable upright posture and steady walking.

From our point of view precisely during this period conditioned reflex of the vertical body position is formed.

In girls, this process occurs faster than in boys, thus they begin to walk earlier. However, this conditioned reflex (let us call it "vicious"), unfortunately fixes wrong position of the body tilted to the right or to the left. This child comes to life and remains the same in subsequent periods of his/her life, unless he/she will meet a competent orthopaedist!

Thus, why do anatomists consider body curvature to be normal? Indeed, it is typical for every human.

Thus, giving answers to the questions raised earlier, we may conclude that the asymmetry of the body occurs due to specifics of brain functioning and its development; asymmetry begins to form already at the fetal stage. Newborn baby already has asymmetry of the trunk muscles. Later, when he/she begins to walk due to different degree of tension of the spinal extensors on the left and the right sides leads to the development of the lateral spinal curvature, which should be called physiological scoliotic posture or functional scoliosis.

As for the degree of body distortion and the transition from physiological to pathological state (scoliotic disease), it depends both on the tone of the trunk extensors and on the structural features of the spine, which are genetically determined. Increasing shortening of one of the lower extremities plays significant role in the progression of deformation. In this case, we don't consider a variety of specific and nonspecific pathological processes that may affect the structure of the musculoskeletal system.

The above said allows to conclude that since the intrauterine period of human development up to birth only cerebral mechanism acts to provide the development of lateral curvature of the spine. However, after birth other than cerebral factors are involved. Various theories of the etiology of scoliosis are based on the analysis of these factors, which we have discussed earlier.

It should be mentioned that many scientists have tried to investigate the nature of the asymmetry of the body. One of these was of considerable theoretical and practical interest and answered on one of the questions stated above: what comes first – lateral curvature or muscle asymmetry (**15**). The author experimented on young monkeys, aged from 1 to 1.5 years. Surgery consisted of unilateral extirpation of the common trunk extensor (m. erector trunci) from the sacrum to the lower part of the chest. In a month lateral curvature of the spine has developed. During subsequent 3-4 weeks wedge-shaped vertebrae appeared as a result of asymmetric growth. Radiographic picture was the same as in humans with scoliosis. Thus, according to the investigator, the primary cause of the development of scoliotic deformity in experimental animals was unilateral spasm of the preserved common spinal extensor, which caused pelvic tilt toward weak muscles.

Other investigators also pointed at the significance of contractures of spinal muscles as one of the first signs of scoliosis progression in infancy (**12**).

Importantly, we have come to this conclusion by ourselves, while examining the spines of breastfed children.

On 11th International Symposium on Scoliosis (London, 2006) several reports on the same issue were presented. Particularly, an association was found between adolescent IS and asymmetric anatomy and function of the cerebral and cerebellar hemispheres (**7, 10**).

An experimental porcine model of unilateral paralysis of spinal extensors was created using toxin of Clostridium botulinum. This caused lateral curvature of the spine in thoracic region on the side of paralyzed muscles. Another investigators have suggested that the primary cause of IS and associated spinal pain is impaired balance of muscles supporting the spine, which is in turn caused with the different activity of cerebral hemispheres (8, 9).

Contemporaneously, other possible causes of spinal deformities were studied, particularly, the effect of gravity on the body position in space and development of curvatures and anti curvatures of the spine (**3, 4**). The authors have presented their point of view on the causes of IS:

1. Progressive unilateral contracture of paravertebral muscles observed in scoliosis already in infancy provides a basis for structural changes of the spine.
2. Development of structural scoliosis is the result of asymmetric growth of vertebrae.
3. With the beginning of walking even a slight curvature of the spine immediately impairs its dynamic equilibrium. On the concave side of the curvature pressure is higher compared to the convex side.

We remind the reader that according to law of Hueter-Volkmann, areas of bone where epiphyseal cartilage is exposed to severe and prolonged compression grow slower and less loaded areas of epiphyseal cartilage, therefore, provide acceleration of bone growth. Thus wedge-shaped vertebrae are formed. With increasing curvature arc of the thoracic spine, the forces of vertical load are also increasing, thus suppressing epiphyseal growth of vertebrae on the concave side.

In this way, prolonged and increasing asymmetric load on the spine during the period of active growth of the skeleton, especially in cases of progressive scoliosis, creates so-called “vicious circle”. Its essence is in the fact that increasing pressure potentiated wedge-shape deformity of vertebrae and this leads to increasing deformation of the spinal segment, which in turn causes even greater asymmetrical load.

Other researchers have come to conclusions regarding the signifi significance of gravity in the formation of curvatures and anti curvatures of the spine (**2, 6**). At the same time the important role of degenerative changes of intervertebral discs was emphasized, which is clearly seen during postnatal development and even earlier – during intrauterine period. Finally, Australian investigators (11) came to the conclusion that gravity-associated tilting of the body (of the spine) is a potential cause of rotational displacement of vertebrae in IS.

Summarizing the given material on the etiology of IS it may be concluded that a man is born with rotated vertebrae as a result of asymmetry of spinal extensors. But when he/she begins to walk, further progression of rotation of separate vertebrae and their groups is potentiated with the forces of gravity; this is the main cause of initially physiological

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curvature and then pathological deformation of the spine. This is the nature of the spinal mechanism of development of the lateral curvature of the spine.

So, we have given answers on all the questions stated above. There is only one uncertainty remained – what made vertebrae to rotate relative to each other in all regions of the spine (cervical, thoracic, lumbar and sacral)? Why lateral flexion of the spine inevitably lead to their rotation and torsion? To answer these questions we have studied the biomechanical aspects of vertebral torsion. The essence of the study is presented below (the section was written in collaboration with Associate Professor of Theoretical Mechanics and Mechanical Engineering of Odessa National Polytechnic University, PhD in Technical Sciences, Svinarev YN).

Rotatory displacement of vertebrae relative to each other in spine bending – justification from biomechanical perspective

According to the laws of mechanics, an object will remain stable only if the projection of its center of gravity lies within the area delineated by the bearings of the object (**Fig. 5**). The object shown in Fig. 5a will be stable, and the object in Fig. 5b – will tip over. This statement remains applicable to biomechanics of the human body.

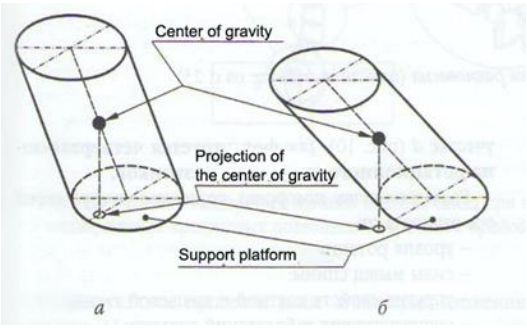

Figure 5: Center of gravity, projection of center of gravity, supporting site. **A-** stable object, **B–** unstable object.

Cerebellum and vestibular apparatus of the inner ear, which control the vertical position of the body and its movements in space, projects center of gravity within the supporting area bounded by feet in order to provide maximum stability of the body (**Fig. 6**).

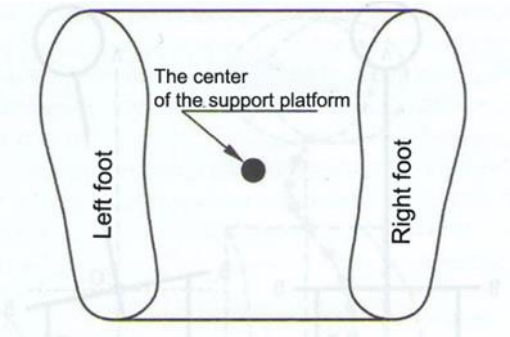

Figure 6: Supporting site. Center of supporting site, left feet, right feet

In bending of the trunk and pelvic tilt caused with an absolute and (or) relative shortening of the leg axis of the spine (**Fig. 7a**) deviates from the vertical axis, shifting the center of gravity towards the tilt (**Fig. 7b**).

At the same time, spinal muscles bend the spine in a direction opposite to the deviation of the center of gravity in order to preserve balance (**Fig. 7c**).

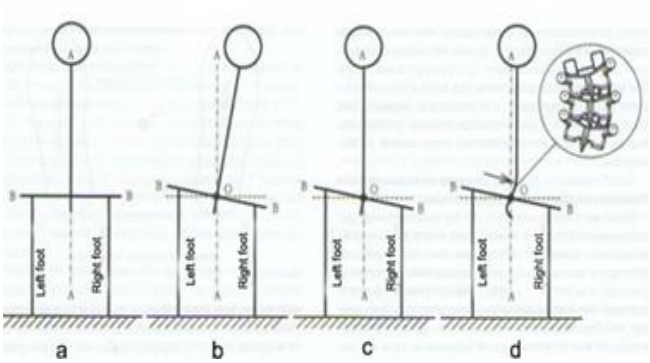

Figure 7. Curvature of the spine without impairment of balance.

If the tilt could be counterbalanced with rotation of only one vertebra in a vertical plane then the spine would acquire vertical position bending at the point O, as shown on **Fig. 7c**; the center of gravity would return to the axis of symmetry A-A and stability of the body would be restored and the spine above the point O would preserve its straightness.

In fact, possible relative motions of vertebrae allow the spine to bend to a desired angle only through simultaneous rotation of a few adjacent vertebrae (**Fig. 8a**). As a result, the spine bended in the region c over some radius rc and acquires a vertical position, will not return the center of gravity on the axis of symmetry A-A (**Fig. 7d**). So in reality in the region c the spine rotates at a greater angle so that the axis of the spine intersects the vertical line A-A (**Fig. 8a**).

At the same time the spine being under control of cerebellum and vestibular system tends to acquire vertical position thus bending in the region b over some radius rb (**Fig. 8b**). In this position the center of gravity will be projected close to the center of supportive area, maintaining equilibrium of the body. However, the resulting tilt is not physiological, so it is reflexively corrected through bending of the spine in the region a over some radius ra (**Fig. 8c**), and the head also reflexively tends to turn so that the line of eyes would take maximally horizontal position.

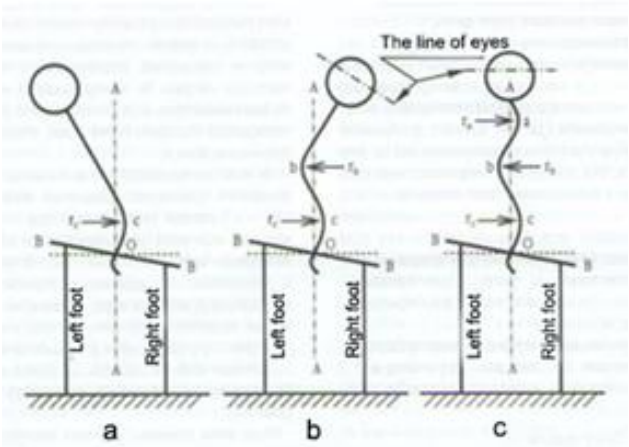

Figure 8. Curvature of the spine with impairment of balance.

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Spinal deformity is not limited only to lateral curvature. Simultaneously separate vertebrae are turning about their axes – that is what we call rotation, resulting in subsequent reversal of separate segments of the spine – its torsion.

Due to the processes described above typical zones of the spine are formed – a, b and c that correspond to cervical, thoracic and lumbar regions where the vertebrae rotate relative to each other in a vertical plane (**Fig. 9**).

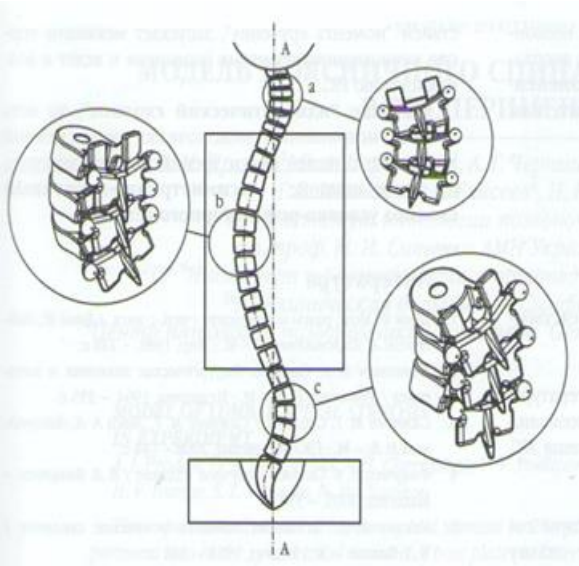

Figure 9. Regions of typical curvatures of the spine in an adult human with anatomically normal sacrum. Shortening of the right leg.

However, considering the fact that in all individuals up to 24 to 25 years of age and in 20-25% of older subjects sacral vertebrae are unfused (lumbarization), in lateral curvature of the spine fifth lumbar and upper sacral vertebrae also rotate relative to each other in some region d (**Fig. 10**). Thus, the forth zone of rotational displacement of vertebrae is formed.

The degree of torsion of vertebrae around their axes depended on:

- The level of rotation;
- Strength of spinal muscles;
- Elastic properties of bony and cartilaginous tissue;
- Comorbid diseases of the skeleton;
- Endocrine dysfunctions, etc.

According to the laws of mechanics ("torsional moment" or torque), in each region of the spine, e.g. cervical, thoracic or lumbosacral, rotational displacement of vertebrae on the top of the curvature of each segment and mutually antithetical displacement of adjacent vertebrae were observed (**Fig. 11**).

These displacements may be explained with the tendency of an organism to preserve vertical position of the body, or, in other words, to ensure stability of the vertical structure – the spinal column. This is the reflection of the basic laws of mechanics.

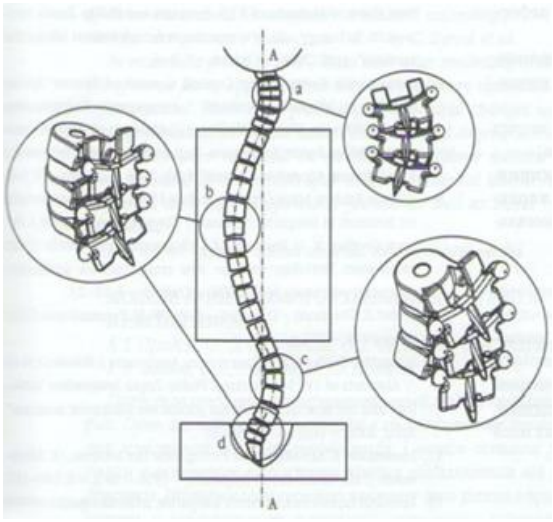

Figure 10. Regions of typical curvatures of the spine in unfused sacral vertebrae. Shortening of the right leg.

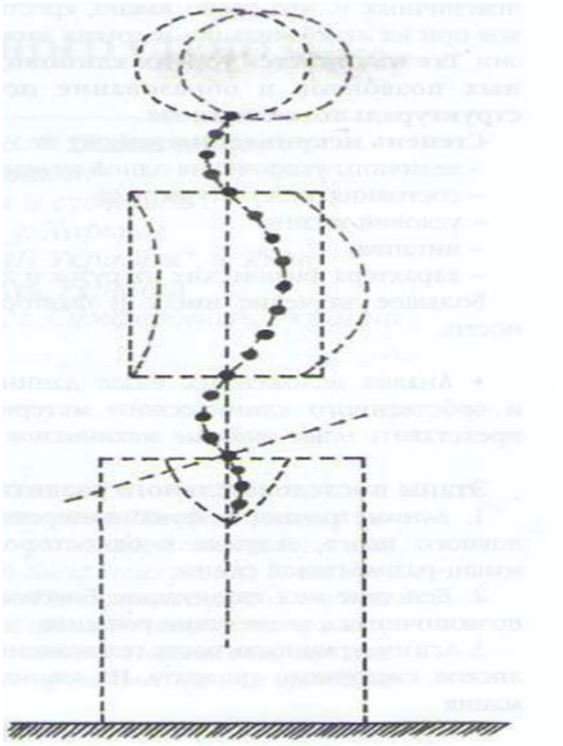

Figure 11. Schematic presentation of changes in body position in lateral bending of the trunk in equal length of lower extremities: •Vertical position of the body in equal length of lower extremities; •Deformation of the body in pelvic tilt due to shortening of the left leg; •Zones of rotational displacement of vertebrae at the top of segment curvature; •Zones of mutually antithetical displacement of vertebrae.

We shall consider another important fact. Already in early childhood and adolescence during the active development of the spinal skeleton in the tilt-rotated position (in zones of its maximal curvature), vertebral bodies and processes, intervertebral discs and ligamentous apparatus acquire an asymmetrical structure. As a result, dynamic stability of the spine is impaired and zones of instability in each segment of the spine are formed.

In turn, formation of these zone of instability leads to the situation when even a small pelvic tilt is sufficient to cause (in accordance with the action of the laws of classical mechanics) rotational displacement of vertebrae in these regions of the spine under the influence of "torsional moment"; then, cervical, thoracic, lumbar, and sacral vertebrae begun to turn around their axes in the presence of lumbarization and other types of dysplasia. Thus, torsion of wedge-changed vertebrae begins and true or structural scoliosis is formed.

Degree of curvature depends on the following:

- Degree of leg shortening;
- Condition of the body musculature;
- Living conditions;
- Nutrition;
- Type of physical activities, etc.

Hereditary factors are also of great importance.

- Analysis of the above data and our own clinical material allowed us to make our own considerations on the mechanisms of IS.

Subsequent stages of is

1. Asymmetrical functioning of cerebral cortex leads to unilateral spasm of spinal extensors.
2. Effect of gravity. Lateral curvature of the spine with elements of rotation.
3. Asymmetric growth of the vertebral bodies, processes, discs and ligaments. Wedge-shaped deformation.
4. Impairment of the dynamic equilibrium of the spine with formation of zones of instability on the top points of the curvatures of each segment.
5. Torsion of vertebrae within the instability zones due to “torsional moment” (laws of mechanics).

This mechanism of development of lateral curvature of the spine has regular nature and does not depend on gender, age and nationality of the patient.

The statement that we have formulated – "Consistent regularity of scoliosis development based on zones of instability in all its regions, occurring as a consequence of unilateral hyper tonus of spinal muscles, which is associated with asymmetric functioning of cerebral hemispheres" was recognized as scientific discovery and was awarded by Ukrainian Academy of original ideas; diploma #5 was issued (21.02.2008).

CONCLUSIONS

1. Idiopathic scoliosis is caused with regular, genetically determined, asymmetric structure of the human body, particularly, the brain.
2. Impairment of dynamic equilibrium of the spine in zones of instability associated with increasing asymmetry of musculature under the influence of “torsional moment” induces torsion of wedge-changed vertebrae and leads to IS.
3. The term “idiopathic scoliosis”, e.g. lateral curvature of the spine of unknown origin, from our point of view should be replaced with other term – “asymmetrically-muscular scoliosis of conditioned reflex origin”.

Author Contributions: LSVV, SAV, TGV: Research of the literature, Patient examinations, Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Bloom F. Brain, Mind and Behavior / F. Blum, A. Leiserson, L. Hofstadter. – M., 1988. – 248p. (Блум Ф. Мозг, разум и поведение / Ф. Блум, А. Лейзерсон, Л. Хофстедтер. – М. : Мир, 1988. – 248 с).
2. Movshovich IA. Scoliosis. Surgical anatomy and pathogenesis / IA Movshovich. - M., Medicine, 1964. – 255pp. (Мовшович И. А. Сколиоз. Хирургическая анатомия и патогенез / И. А. Мовшович. – М. : Медицина, 1964. – 255 с).
3. Sampiev MT. Scoliosis / MT Sampiev, AA Laka, NV Zagorodniy. - M. GEOTAR Media, 2008. – 144pp. (Сампиев М. Т. Сколиоз / М. Т. Сампиев, А. А. Лака, Н. В. Загородний. – М. : ГЭОТАР-Медиа, 2008. – 144 с).
4. Fishchenko VY. Scoliosis: a scientific publication / VY Fishchenko. - Makeevka, 2005. – 550pp. (Фищенко В. Я. Сколиоз : научное издание / В. Я. Фищенко. – Макеевка, 2005. – 550 с).
5. Chaklin VD. Pathological anatomy, clinical features and treatment of scoliosis / VD Chaklin. - M. Medgiz, 1958. – 340pp. (Чаклин В. Д. Патология, клиника и лечение сколиоза / В. Д. Чаклин. – М. : Медгиз, 1958. – 340 с).
6. Schantz AM. Practical Orthopedics: translated from German / AM Schantz. - M. Medgiz, 1933. – 410pp. (Шанц А. М. Практическая ортопедия : пер. с нем / А. М. Шанц. – М. : Медгиз, 1933. – 410 с).
7. Aage Indabl. The role of muscles in the development of scoliosis, an experimental study in a porcine model / Aage Indabl, Sten Holm // Abstracts of 11th International Philip Zorab Symposium “Aetiology and new treatments for adolescent idiopathic scoliosis”. April, 2006. – Oxford. – P. 2-3.
8. Annapoorna Kuppuswamy. Cortical Control of Erector Spinae Muscles in Idiopathic Scoliosis / Annapoorna Kuppuswamy, Peter H. Ellaway, Alison H. McGregor // Abstracts of 11th International Philip Zorab Symposium “Aetiology and new treatments for adolescent idiopathic scoliosis”. April, 2006. – Oxford. – P. 4-5.
9. Clayton J. Adam. Askin Gravity-induced Torsion and Intravertebral Rotation in Idiopathic Scoliosis / Clayton J. Adam, Mark J. Pearcy, Geoffrey N. // Abstracts of 11th International Philip Zorab Symposium “Aetiology and new treatments for adolescent idiopathic scoliosis”. April, 2006. – Oxford. – P. 22-23.
10. Hubel D. The Brain / D. Hubel. – N. Y. : W. H. Freeman and Company. – 1979. – 321 p.

11. Idiopathic Scoliosis and Basicranium Asymmetry / Rousie D. et al. // Abstracts of 11th International Philip Zorab Symposium “Aetiology and new treatments for adolescent idiopathic scoliosis”. April, 2006. – Oxford. – P. 56-57.

12. Lindemann K. Aetiologie und Pathogenese der Scoliose / K. Lindemann // Handbuch der Orthopadie. – 1958. – ¹ 2. – S. 160–187.

13. Perinatal factors in adolescent idiopathic scoliosis – questionnaire study / Chaloupka R. et al. // Abstracts of 11th International Philip Zorab Symposium “Aetiology and new treatments for adolescent idiopathic scoliosis”. April, 2006. – Oxford. – P. 12-14.

14. Schmidt R. F. Human Physiology / R. F. Schmidt, G. Thews. – N. Y. : Springer–Verlag, 1983. – 797 p.

15. Stillwell D. Structural deformities of vertebrae / D. Stillwell // The Journal of bone and joint surgery. – 1962. – Vol. 44-A. – P. 611–634.

Medical Science and Discovery
ISSN: 2148-6832

The clinical, laboratory and prognostic characteristics of haemorrhagic stroke cases related to COVID-19 infection

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ABSTRACT

Objective: Although ischemic and thrombotic vascular processes are more widely reported in COVID-19, the ratio of haemorrhagic cerebrovascular disease is lower. However, it needs to be evaluated because the mortality rate is higher in haemorrhages, and they may appear iatrogenically.

Material and Methods: Patients observed at the Prof. Dr. Cemil Taşçıoğlu City Hospital between March 11th, 2020, and March 11th, 2021, were included in the study. Cases diagnosed as consecutive full intracerebral haemorrhage and concomitant with COVID-19 were observed during the study period. This study is a cross-sectional, retrospective, and observational study.

Results: Within the 1-year period, 11 patients (7 men and 4 women) with a mean age of 64.45±18.68 years related to COVID-19 were recorded. Risk factors were high blood pressure at a frequency of 64%, diabetes mellitus at 45%, and the use of antiaggregants/anticoagulants at 36%. The ratio of male patients was 64% (n=7). The location of haemorrhage was intraparenchymal in 91% (n=10), and subdural in 9% (n=1). The mortality rate was 64%.

Conclusion: Neurologic findings that develop, especially in noncooperating and prone patients in wards and intensive care units, must be observed carefully. Caution must be exercised in prophylactic antiaggregant and anticoagulant treatment, especially in high-risk patients. Intracranial haemorrhages are important due to high mortality.

Keywords: COVID-19; intracranial haemorrhage; haemorrhagic stroke; anticoagulant and antiaggregant treatment; mortality

INTRODUCTION

The correlation between the development of secondary neurologic symptoms in coronavirus disease 2019 (COVID-19) infection and unfavourable outcomes has been emphasised. Parameters such as increased coagulation tests and D-dimer are correlated with increased coagulopathy (**1**). An increased risk of haemorrhage along with a thrombosis risk in these patients has been emphasised (**2**). When evaluating the literature, it is seen that the incidence of haemorrhagic stroke is lower compared with that of ischemic stroke (**3**). It was proved that COVID-19 caused a thrombosis tendency, and treatment protocols were formed accordingly. There exists a tendency to increase antiaggregant and anticoagulant treatment in high-risk patients (**4**). However, the risk of the development of haemorrhage should also be considered. The comorbidities in the patient group, and the antiaggregant and anticoagulant treatments administered in treatment, may cause a tendency towards haemorrhage. Although the clinical findings and treatment approaches correlated with COVID-19-related thrombosis are well established, data relating to haemorrhage are limited.

We evaluated the risk factors, concomitant diseases, haematologic values, and administered treatments of patients diagnosed as having and treated for COVID-19, in whom haemorrhage was found as a result of a neurology consultation. We researched haemorrhage distribution rates and mortality based on imaging findings. We planned this study because we thought it was important to draw attention to data on haemorrhages and identify their causes.

Research Article

Received 26-10-2021

Accepted 20-11-2021

Available Online: 23-11-2021

Published 30-11-2021

http://dx.doi.org/10.36472/msd.v8i11.622

MATERIAL and METHODS

This is a single-centre, retrospective, cross-sectional, observational study. Prof. Dr. Cemil Taşçıoğlu City Hospital is a tertiary multidisciplinary hospital, the emergency room of which serves 500,000-550,000 patients every year. At our hospital, approximately 400 patients present to the emergency room pandemic area daily for suspected COVID-19 infection, and around 40 patients are diagnosed as having COVID-19. According to their clinical presentation and findings, outpatient or inpatient treatment is decided for these patients.

Between March 11th, 2020, and March 11th, 2021, 8500 patients with COVID-19 were found to be receiving treatment as inpatients. From among these patients, the clinical and laboratory data for those receiving treatment due to COVID-19 and were diagnosed as having haemorrhagic stroke based on the clinical picture and computed tomography (CT) scans, and patients with haemorrhagic cerebrovascular disease who were admitted to the hospital during the same period for causes unrelated to COVID-19 and evaluated by the neurology clinic were examined for the study. The patients' demographic data, existing diseases, neurologic examinations at admission, electrocardiogram (ECG), routine blood analyses [lymphocytes, leukocytes, platelets (PLT), C-reactive protein (CRP), fibrinogen, D-dimer, procalcitonin, activated partial thromboplastin time (aPTT)], and cranial imaging (CT) were recorded. The medication the patients used, especially their antiaggregant and anticoagulant use, was recorded. Concomitant comorbidities were recorded. Their haemorrhage locations were evaluated. Response to treatment and disease outcome data were recorded. Ethical approval for the study was obtained from the Ministry of Health and the Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital ethics board (Approval No.: 31 of 26.01.2021). The study conformed to the Helsinki Declaration.

Statistical Examinations: The NCSS (Number Cruncher Statistical System) (Kaysville, Utah, USA) software was used for statistical analyses. Complementary statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used when evaluating the study data. The suitability of quantitative data to normal distribution was tested using the Kolmogorov-Smirnov, Shapiro-Wilk test, and graphic evaluations. Student's t-test was used in two-group comparisons of quantitative data presenting normal distribution, and the Mann-Whitney U test was used in two-group comparisons of data without normal distribution. Pearson's Chi-square test was used in comparing qualitative data. Significance was considered at a minimum of $p<0.05$.

RESULTS

Fifty patients with COVID-19-negative haemorrhage and 11 patients with COVID-19-positive haemorrhage receiving inpatient treatment in inpatient wards were recorded between March 11th, 2020, and March 11th, 2021. Among the patients who were COVID-19-negative, there were 17 women and 33 men, with a mean age of 62.88±8.78 years. Among the patients who were COVID-19-positive, there were four women and seven men, with a mean age of 64.45±18.68 years. The demographic data for patients who were COVID-19-positive are presented in Table 1. There was no statistical difference in terms of age and sex between the two groups ($p=0.80$). Haematologic data were evaluated in the two groups according to their distribution between the groups. No difference was found between the groups in terms of parametrically distributed PLT values ($p=0.377$). The haemoglobin (Hb) value was found to be statistically significantly lower in the COVID-19-positive group ($p=0.012$). No difference was found between the two groups in terms of the neutrophil, lymphocyte, leucocyte, INR, and neutrophile/lymphocyte ratios, which were seen to be distributed nonparametrically. The biochemical values and coagulopathy values of the COVID-19-positive cases are presented in (**Tables 2** and **3**).

The use of antiaggregants/anticoagulants was found to be significantly higher in the COVID-19-positive group ($p=0.02$). Twenty-two of 50 of the COVID-19-negative group were using antiaggregants and anticoagulants. Eleven patients were receiving ASA, six were receiving next-generation anticoagulants (NOAK), two had coumadin, and two patients were receiving dual treatments (ASA+clopidogrel, rivaroxaban+clopidogrel). Forty-two per cent of this group received treatment.

Seven of 11 of the COVID-19-positive group received antiaggregants and antiaggregants/low-molecular-weight heparin. In the term before hospitalisation, three were receiving acetylsalicylic acid (ASA), and one was receiving clopidogrel. This amounted to 36% of the patient group. The treatment of three patients was started at admission. The distribution of the medication taken by the patients is presented in Table 4.

Table 1. Comparison of demographic and hematologic data of COVID positive and negative cases

	COVID-19 negative n=50	COVID-19 positive n=11	P value
Age	62.88±18.76	64.45±18.68	0.804
Sex (Female/Male)	17/33	4/7	0.881
Drug abuse (-/+)	28/22	4/7	**0.002**
Survey (in life/exitus)	36/14	4/7	**0.027**
Platelets	224.000±70119	194.727±101635	0.377
Haemoglobin	13.3±2.2	10.2±3.2	**0.012**
WBC	951 (300-2866)	878 (144-2177)	0.155
Neutrophil	723 (29-2313)	697 (149-2084)	0.195
Lymphocyte	122 (13-871)	132 (59-430)	0.136
Neutrophil/Lymphocyte ratio	4.87 (0.24-84.83)	5.02(2.06-15.79)	0.195
INR	1.09 (0.87-4.94)	1.13 (0.80-1.48)	0.180

WBC: White blood cell, INR: International Normalised Ratio

http://dx.doi.org/10.36472/msd.v8i11.622

Table 2. Hematologic values

Case no.	WBC /µL	Neutrophil /µL	Lymphocyte /µL	Hb g/L	PLT /µL	D-dimer ug/L	CRP mg/L	INR	aPTT
Normal values	3800-10,000	1780-5380	1320-3570	130-175)	150,000-400,000	80-500	<5	0.8-1.2	
1	7360	6810	330	133	28,000	8120	223	*1.13*	24
2	12,000	8910	430	108	143,000	1050	93	1.18	26
3	1896	15,220	1520	113	289,000	4040	13.68	1.2	34.7
4	8780	6230	820	130	202,000	680	91.1	1.01	24
5	8250	6970	740	134	202,000	332	34	0.9	21.1
6	11,000	10,320	1240	85	280,000	1480	101.6	1.48	31.3
7	1440	1490	590	91	18,000	850	121.6	1.0	31.7
8	21,770	2084	1320	62	350,000	1190	253.6	1.36	10.79
9	7930	3520	700	107	195,000	2110	93	0.8	21
10	6100	4820	1640	158	208,000	240	148	1.24	31.6
11	14,560	12,610	1070	148	227,000	-	9.52	1.03	19.6

WBC: leukocyte, Hb: haemoglobin in blood count, Hct: haematocrit, PLT: thrombocyte, CRP: C-reactive protein

Table 3. Coagulopathy values

Case no	Ferritin	D- dimer	Procalcitonin	Fibrinogen	Urea	ALT	AST	LDH
1	*	8120	37	523	41	73	93	432
2	235.6	1050	*	*	117	69	82	*
3	1661	4040	0.5	*	54	25	16	531
4	257	0,68	0.72	483	19	14	33	188
5	129	332	0.32	*	23	94	37	745
6	861.9	1.48	0.07	519	125	12	13	217
7	*	85	0,4	453	32	270	91	256
8	4194	119	119	791	117	22	41	273
9	*	2110	*	*	72	10	17	*
10	2827	24	6	602	17	*	*	317
11	*	*	*	*	31	17	24	306

*No data

Table 4. Antiaggregant/anticoagulant distribution ratios by groups

	Group		
	COVID-	**COVID+**	**Total**
Absent	28	4	32
Antiaggregant	13	4	17
Anticoagulant	8	0	8
Anticoagulant and Antiaggregant	1	0	1
Antiaggregant and Enoxaparin	0	3	3
Total	50	11	61

Table 5. Haemotoma location

		Group		Total
		COVID -	COVID +	
Hematoma location	Putaminocapsular	8	1	9
	Thalamic	6	0	6
	Pons	5	1	6
	Lobar	14	6	20
	SAH	6	0	6
	Subdural	9	1	10
	Infratentorial	2	2	4
Total		50	11	61

SAH: subarachnoid hemorrhage

The most frequent comorbidity in the COVID-19-positive group was hypertension (HT) with 64%, followed by diabetes mellitus (DM) with 45%. Other comorbid diseases were ischemic heart disease, chronic obstructive pulmonary disease (COPD), chronic kidney failure, benign prostate hypertrophy, renal cell carcinoma, and glioblastoma multiforme. The first and second most frequent risk factors we identified in the COVID-19-negative patient group were HT (27/50) (54%) and DM (11/50) (22%). These were followed by concomitant coronary artery disease and trauma. Other risk factors were vascular malformation, polycythaemia vera, COPD, brain tumours, and cardiomyopathy.

There was no significant difference in terms of risk factors between the groups (p=0.443). Although not statistically significant, vascular malformation and traumatic subarachnoid haemorrhage (SAH) in the aetiology in the negative group were also noteworthy.

The haemorrhage distribution rates between the two groups are presented in the table. No difference was identified between the groups in terms of distribution location (p=0.232) (Table 5). No difference was found between the groups in terms of clinical presentation (p=0.671) (**Fig 1**, brain CT images of 11 COVID-19-positive cases).

http://dx.doi.org/10.36472/msd.v8i11.622

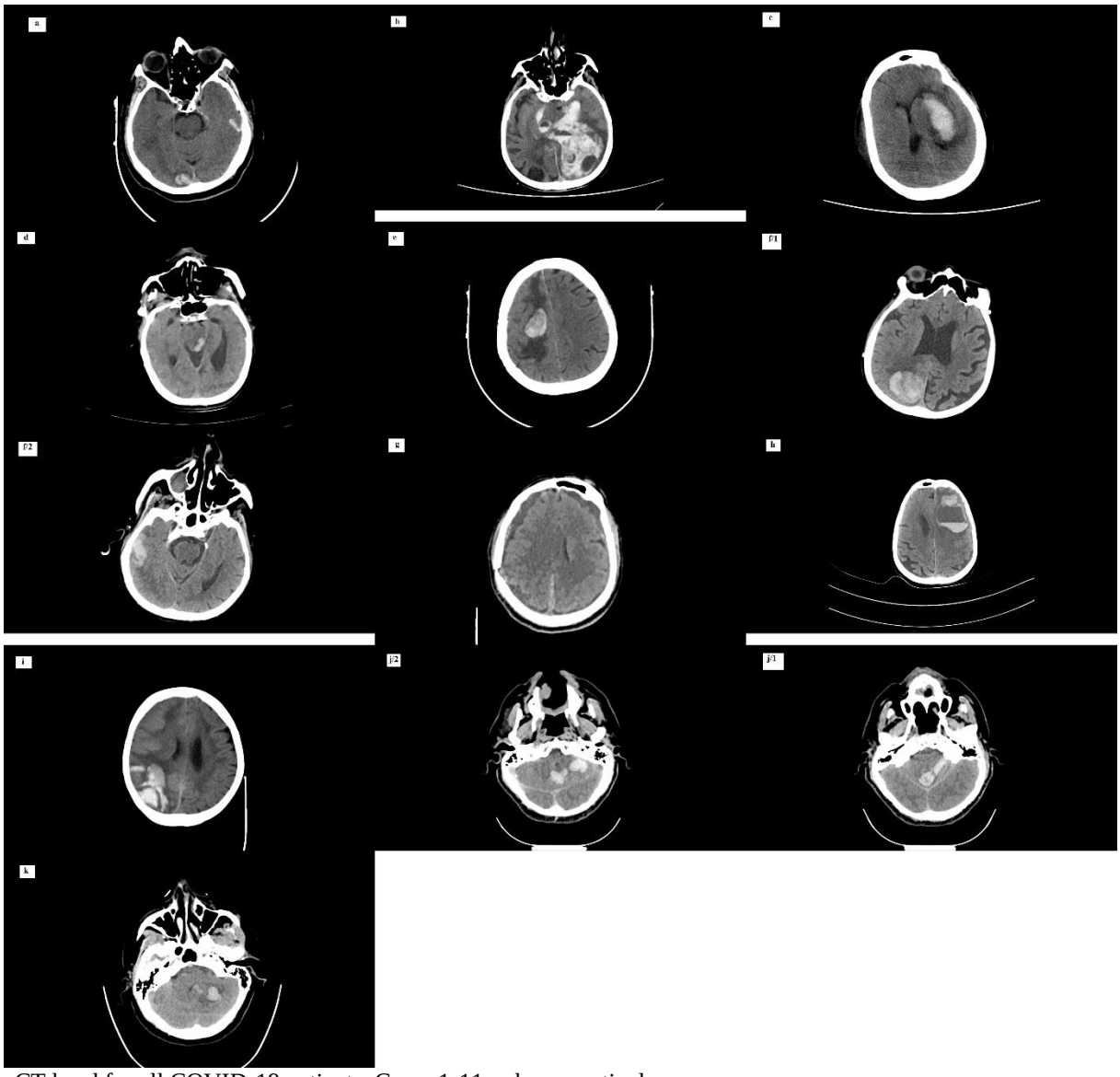

Fig 1: CT head for all COVID-19 patients. Cases 1-11, a-k, respectively.

The time between the diagnosis of patients with COVID-19 and the onset of haemorrhage varied between 0-15 days. Six of 11 (55%) of our patients presented primarily with symptoms of haemorrhage, which was concurrent with the COVID-19 diagnosis. The haemorrhage time was day 0 of the presentation to the hospital in three patients using anti-ischemic treatment, and the 10th day in one patient.

A significant difference was found between the groups in terms of mortality rates (p=0.024); the mortality rate was 64% in the COVID-19-positive group, whereas it was 28% in the negative group.

DISCUSSION

Haemorrhagic presentation concomitant with COVID-19 is infrequent but has serious consequences. In 1200 cases observed over 65 days, Pavlov et al. reported the rate of haemorrhage as 0.25% (**5**). In their study, Rothstein et al. reported the rate of ischemia as 2.4%, and the rate of haemorrhage as 0-9% (**6**). Our rate was 0.12%. We had a haemorrhage rate lower than that in the literature. We considered that this was due to our more precautious approach to administering anti-aggregant treatment.

Our clinical approach involves administering anticoagulant doses mostly at prophylactic doses without rising to therapeutic doses. The sex distribution was consistent with that in the literature, where the majority of patients with COVID-19 with intracranial haemorrhage (ICH) were male (65.8%) (**3**). Our cases also mostly consisted of men (64%).

Although haemorrhage is seen less infrequently compared with ischemia in COVID-19, its mortality rate is higher. Severe pulmonary involvement also exacerbates negative outcomes. A mortality rate of 48.6% was reported in patients with COVID-19 with ICH. The mortality rate in our patients was found as 64%. Therefore, it was somewhat high compared with mortality associated with haemorrhages due to other causes (28%). Patients may present with a haemorrhage clinic without presenting pulmonary findings (**7**). This rate was 55% in our patients. Although COVID-19 is not associated with direct traumatic haemorrhages, dizziness and loss of balance associated with COVID-19 is the most reported neurologic finding, and traumatic secondary events may develop. During the pandemic, haemorrhages must be approached with caution considering that there may be an underlying COVID-19 infection, even if the aetiology is trauma. No SAH was seen in the study conducted by

Altschula et al (7). No SAH was observed in our study either, and there were no patients with trauma in their aetiologies.

In our study, we evaluated major haemorrhages identified through brain CT scans. We did not include microhaemorrhages or minor haemorrhages developing from ischemia. Also, no magnetic resonance imaging scans were taken for these diagnoses in these patients (8). Multifocal and multicompartmental ICHs were observed concomitant with more severe COVID-19 findings. These were associated with multiple organ failure, disseminated intravascular coagulation, and iatrogenic anticoagulant use. The risk of haemorrhage must be considered when prescribing anticoagulants in treatment regimens (9). Dogra et al. presented 33 patients with ICH, all of whom were receiving anticoagulants at therapeutic doses (9). Only four of our patients were receiving antiaggregant during their inpatient treatment, and no oral anticoagulants were administered. This may be interpreted as an illustration of the contribution of the vascular impacts of COVID. Patients developing haemorrhages in the course of the COVID-19 treatments after admission were receiving enoxaparin sodium 4000 IU, 6000 IU or 8000 IU in addition to ASA 100 mg. It was observed that haemorrhage appeared on the 8-15th days of this treatment. The most frequent comorbidity was HT. The second most frequent was DM. This distribution was similar to haemorrhages not concomitant with COVID-19. This led us to believe that greater care should be taken in the dosages and durations in administering antithrombotics/antiaggregants to patients with diabetes with a high risk of haemorrhage, especially those who have high blood pressure, or unregulated arterial pressure and blood sugar.

In a case reported in the literature, a patient receiving a combination of ASA and clopidogrel was administered a therapeutic dose of enoxaparin. This caused the development of a haemorrhage that resulted in mortality in the patient. The coadministration of anticoagulant treatment in those receiving antiaggregants must be carefully considered. A brain CT scan must be obtained before beginning the triple treatment, and proper blood pressure control must be ensured (10). Very severe ICH resulting in brain death was observed in three patients in whom anticoagulants were used in therapeutic doses. All cases resulted in brain death (11).

Also, during the pandemic, arteriovenous malformation, cavernous malformation, dural arteriovenous fistula, cerebral sinus tumours, and brain tumours that could be secondary ICH causes, should not be ignored. Not all haemorrhages that are observed are COVID-19–related (12). Like everywhere in the world, elective surgery could not be performed in Turkey during the pandemic. Many surgeries were postponed due to the shortage of beds in intensive care units (ICUs). The data we reported were evaluated from patients brought to the hospital. Work was performed under extraordinary circumstances during the pandemic. Along with minor cases that did not reach the hospital due to the pandemic, we also believe that there were deaths outside the hospital associated with severe neurologic findings.

Post-mortem brain studies have also shown direct invasion of neurons and glial cells (13). It was emphasised that D-dimer levels were five times higher in ICH in hospitalized patients with COVID-19 (14). In 73% of our patients, D-dimer was found to be high in the range of 1.5-8 times. The necessity to evaluate the risks and benefits of an anticoagulant treatment regimen has been emphasised in a series of six cases in which haemorrhage developed under intensive care. It is also indicated that a change in the neurologic condition may be noticed belatedly in such patients due to reasons such as isolation and sedation (14).

Wang et al. showed an association of a high neutrophil-lymphocyte ratio (NLR) with 30-day mortality in patients with ICH and various studies that indicated that NLR might be an independent predictor of ICH outcomes (15). COVID-19 produces an inflammatory cascade, and a higher NLR at hospital admission has been associated with a more severe outcome (16). In our patient group, in six of the seven cases ending in mortality, NLR was found to be 7.5-20 times higher. However, this rate was not statistically different from the COVID-19-negative cases. Among the haematologic parameters that were evaluated, only the Hb value was found to be significantly lower in the positive group. However, the correlation of this low value with the survey was not identified.

COVID-19 has been documented to enter vascular endothelium, leading to endotheliitis, which could trigger the microthrombosis of small penetrating arteries, and lead to an increased risk for ICH (17-18). In one retrospective study, thrombocytopenia with platelet counts of <150,000 /L and elevations in D-dimer of >2500 ng/mL at initial presentation were also predictive of bleeding complications during hospitalisation (19). In our patients, bleeding was seen even without such high D-dimer values. Only two of our patients presented an outcome above that value. Early-stage COVID-19 CRP levels are known to positively correlate with lung involvement and may reflect disease severity (20). The CRP values of all our patients were high, and involvement was present in thoracic CT in all patients.

Some mechanisms can be considered in the tendency of these patients to develop subdural haemorrhage SDH. The point of entry for COVID-19 into human tissue is mediated primarily by a specific cellular receptor, angiotensin-converting enzyme 2 (ACE-2). In our series, subdural haemorrhage was seen in one case. With respect to bleeding distribution rates in a study evaluating haemorrhages, single compartments were involved in the rest, with intraparenchymal haemorrhage (IPH) being the most common variety (62.6%), followed by SAH (15.0%), SDH (11.6%), and intraventricular haemorrhage (IVH) (1.4%) (3). In a study evaluating 18 patients, proof of acute intracranial bleeding was found within 11 days following presentation (IQR: 9-29). Six (33.3%) patients presented with parenchymal bleeding, 11 (61.1%) presented with SAH, and one (5.6%) patient presented with subdural bleeding. Three patients presented with IVH (16.7%) (21). In addition to there being limited data in the literature, different results have also been reported in terms of haemorrhage location. Except for one, all 11 of our cases had intraparenchymal bleeding.

The limitation of our study is that it is a retrospective, cross-sectional, and single-centre study. The patients included in the study had major bleeding identified through CT scans. No magnetic resonance scanning was performed, and no incidence study was performed from among all patients with COVID-19.

CONCLUSIONS

Although less frequent compared with ischemic cerebrovascular events, it is important to identify ICHs because they present a higher mortality rate. Independent of the use of antiaggregants, the presenting symptom in patients with COVID-19 may be haemorrhage, and the haemorrhage and COVID-19 diagnoses may be concurrent. Caution must also be exercised concerning haemorrhage in inpatients using anticoagulants at a prophylactic dose. Neurologic examination findings must be monitored carefully in clinics and ICUs, and the risks to which the patients are subjected concerning the choice and doses of antiaggregant/anticoagulant treatment must be evaluated; the risk/benefit ratio must be carefully considered.

Author Contributions: SÜÖ, CE: Research of the literature, Patient examinations, Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
2. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet Haematol 2020;7:e362-e363
3. Cheruiyot I, Sehmi P, Ominde B, Bundi P, Mislani M, Ngure B, Olabu B, Ogeng'o JA. Intracranial hemorrhage in coronavirus disease 2019 (COVID-19) patients. Neurol Sci 2021; 42:25–33
4. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135 (23): 2033–2040.
5. Pavlov V, Beylerli O, Gareev I, Torres Solis LF, Solís Herrera A and Aliev G. COVID-19-related intracerebral hemorrhage. Front. Aging Neurosci.2020; 12:600172. doi: 10.3389/fnagi.2020.600172
6. Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL, Acute Cerebrovascular Events in Hospitalized COVID-19 Patients. Stroke. 2020;51:e219–e222.
7. Altschula DJ, Undaa SR, Garza Ramosa RL, Zampolinb R, Bentona J, Hollanda R, Fortunela A, Haranhallia N. Hemorrhagic presentations of COVID-19: Risk factors for mortality Clinical Neurology and Neurosurgery 2020;198 106112
8. Radmanesh A, Derman A, Lui YW, Raz E, Loh JP, Hagiwara M, Borja MJ, Zan E, Fatterpekar GM, COVID-19–associated Diffuse Leukoencephalopathy and Microhemorrhages. Radiology 2020; 297:E223–E227
9. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, Lewis A, Melmed K, Hochman K, Horwitz L, Galetta S, Berger J, Hemorrhagic stroke and anticoagulation in COVID-19Journal of Stroke and Cerebrovascular Diseases,2020; 29(8) 104984
10. Bhanu Gogia, Xiang Fang, Prashant Rai Intracranial Hemorrhage in a Patient With COVID-19: Possible Explanations and Considerations cureus 2020; 12(8): e10159. DOI 10.7759/cureus.10159
11. Ghani MU, Kumar M, Ghani U, Sonia F, Abbas SA. Intracranial hemorrhage complicating anticoagulant prophylactic therapy in three hospitalized COVID-19 patients Journal of NeuroVirology 2020; 26:602–604
12. Montemurroa N. Intracranial hemorrhage and COVID-19, but please do not forget "old diseases" and elective surgery Brain, Behavior, and Immunity 2021;92 207–208
13. Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocrit Care 2020.
14. Fady Mousa-Ibrahim FM, Berg S, Od`TPDetola O, Teitcher M, Ruland S, Intracranial Hemorrhage in Hospitalized SARS-CoV-2 Patients: A Case Series Journal of Stroke and Cerebrovascular Diseases 2021:30 (1) 105428
15. Wang F, Wang L, Jiang TT, Xia JJ, Xu F, Shen LJ, et al. Neutrophil to-lymphocyte ratio is an independent predictor of 30-day mortality of intracerebral hemorrhage patients: a validation cohort study. Neurotox Res 2018.
16. Ciccullo A, Borghetti A, Zileri Dal Verme L, et al. Neutrophil- to-lymphocyte ratio and clinical outcome in COVID- 19: a report from the Italian front line. Int J Antimicrob Agents 2020;56(2):106017.
17. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/ encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55-58.
18. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395 (10234):1417-1418.
19. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136(4):489-500. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136(4):489-500.
20. Wang, L. C-reactive protein levels in the early stage of COVID- 19. Med. Mal. Infect.2020 50, 332–334.
21. Nawabi J, Morotti A, Wildgruber M, Boulouis G, Kraehling H, Schlunk F et al. Clinical and imaging characteristics in patients with SARS-CoV-2 infection and acute intracranial hemorrhage. J Clin Med 2020 9(8):2543

Medical Science and Discovery
ISSN: 2148-6832

Abdominal wall skin lesions in adult morbid obese women

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ABSTRACT

Objective: To present only skin lesions in the abdominal wall that we detected in morbidly obese patients and to examine them in the light of the literature.

Material and Method: Patients who applied to the general surgery outpatient clinic for bariatric surgery and who also had dermatological complaints and were referred to the dermatology outpatient clinic with the detection of skin-related complaints were retrospectively evaluated in terms of age and breast skin findings. Normal skin findings were separated into intertrigo, chronic recurrent folliculitis, eczemas, acanthosis nigricans and striae.

Results: A total of 60 obese female patients were included in the study. The mean age of the patients was 32.4 ± 8.8 years (19-53), and the mean body mass index was 42.6 ± 2.4 (40-49). Normal skin findings were present in 28.3% of the patients (17 patients). The most common finding was striae, and 60% (36 patients) had it. Then respectively, intertrigo was detected in 14 patients (23%), chronic recurrent folliculitis in 12 patients (20%), eczema in 5 patients (8.3%), and acanthosis nigricans in 2 patients (3.3%).

Conclusion: The most common findings on the abdominal wall skin of obese individuals are striae and intertrigo, and similar findings have been found in many studies in the literature.

Keywords: Skin findings, obesity, abdominal wall skin

INTRODUCTION

Morbid obesity is one of the most common health problems that we encounter today. The definition and grading of obesity is made on the basis of the body-mass index (BMI = Weight [kg] / Height [m^2]). Morbid obesity is an outcome of body mass index value of 40 kg/m^2 or higher. Its incidence has increased gradually over the years, and unfortunately it continues to increase worldwide (**1, 2**).

Obesity should not be considered as a single disease and it should be known that it is associated with many comorbid diseases. It may cause many important health problems such as hypertension, diabetes, obstructive sleep apnea syndrome, cardiovascular diseases and increased cancer risk, as well as aesthetic concerns, especially in young female individuals.

Obesity seriously disrupts the basic functions of the skin, such as barrier functions, sebaceous gland activities and fat production, sweat production, lymph system flow, skin's collagen structure and functions, wound healing, blood circulation and subcutaneous adipose tissue. In these people, the permeability functions of the skin deteriorate and the skin dries out as it loses moisture, and irritation, redness and cracking may occur more due to this drying. It also creates susceptibility to maceration and other opportunistic infections due to prolapse (**3, 4**).

There are a few studies in the literature that examine the skin findings seen in obese patients. Complaints and findings of obese individuals were discussed in these studies (**5, 6).** In our study, we present only skin lesions in the abdomen wall that we detected in morbidly obese patients and examine them in the light of the literature.

Research Article

Received 11-11-2021

Accepted 22-11-2021

Available Online: 24-11-2021

Published 30-11-2021

http://dx.doi.org/10.36472/msd.v8i11.624

MATERIAL and METHODS

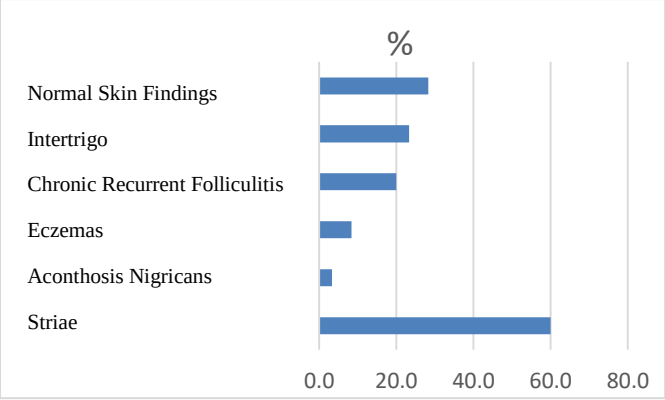
Patients who applied to the general surgery outpatient clinic for bariatric surgery between August-2018 and November-2021 and who also had dermatological complaints and were referred to the dermatology outpatient clinic with the detection of skin-related complaints were evaluated retrospectively. The data were evaluated from computer records and outpatient clinic doctor records. The patients were examined by the same consultant clinician.

The patients were evaluated in terms of age and abdominal wall skin findings. The patients were separated as normal skin findings, intertrigo, chronic recurrent folliculitis, eczema, acanthosis nigricans and striae. This study was conducted in accordance with the Helsinki Declaration Principles. The data were evaluated with the Statistical Package for IBM SPSS Statistics 22.0 program, and the statistics were given as a percentage (%), frequency (n), mean ± standard, deviation minimum and maximum values.

RESULTS

A total of 60 obese female patients were included in the study. The mean age of the patients was 32.4 ± 8.8 years (19-53) and the mean body mass index was 42.6 ± 2.4 (40-49). Normal skin findings were present in 28.3% of the patients (17 patients). The most common finding was striae, and 60% (36 patients) had it. Then respectively, intertrigo was detected in 14 patients (23%), chronic recurrent folliculitis in 12 patients (20%), eczema in 5 patients (8.3%), and acanthosis nigricans in 2 patients (3.3%).

There were lesions in two different diagnoses in 16 patients and in 3 different diagnoses in three patients. Graphic 1 shows normal skin findings and percentage distribution of lesions. Table 1 shows the numerical distribution of skin lesions.



Graph 1. Normal skin findings and percentage distribution of lesions

Table 1. Numerical distribution of skin lesions

		n	%
Striae	None	24	40.0
	Yes	36	60.0
Acanthosis nigricans	None	58	96.7
	Yes	2	3.3
Eczemas	None	55	91.7
	Yes	5	8.3
Chronic recurrent folliculitis	None	48	80.0
	Yes	12	20.0
Intertrigo	None	46	76.7
	Yes	14	23.3
Normal skin findings	None	43	71.7
	Yes	17	28.3

DISCUSSION

Obesity, which means an excessive amount of adipose tissue in the body and is one of the oldest diseases of humanity, is increasing rapidly today (7). Obesity brings along many chronic metabolic diseases. In addition to these diseases that adversely affect human health, chronic and acute skin diseases associated with obesity are ignored (8).

Obese patients are at a higher risk of skin integrity deterioration compared to normal-weight patients. In this patient group, different skin diseases occur due to the barrier function of the skin, sweat glands, lymphatic circulation, deterioration in collagen functions, delay in wound healing, impairment of micro and macrocirculation, and changes in subcutaneous adipose tissue. Additionally, some dermatological diseases such as striae distensae, lymphedema, chronic venous insufficiency, adiposis dolorosa, hyperkeratosis, recurrent skin infections and psoriasis are also associated with obesity (7-11).

Since no comparison was made with normal non-obese people in this study, we do not know what the ratio of abdominal wall skin findings we detected to normal individuals. In our study, we examined only abdominal wall skin lesions in obese individuals. We could not find a study similar to this one in the literature. Thus, we made our comparisons with studies on obese individuals.

The most common finding we observed was striae with a rate of 60% patients. Striae are line-like scars that occur in the areas of the body that are most exposed to skin tension with the weakening of the supporting tissues of the dermis. Studies are most often found in the breasts, buttocks, abdomen, and thighs. In a study conducted on obese children, they detected 40% striae (12). In another study where a comparison was made on 510 obese individuals, 62% of striae were detected, and they found the rate of striae statistically higher in obese patients compared to the control group (6). In our study, in accordance with the literature, the most common finding was stria.

Studies have found that there is a linear trend between the severity of obesity and intertrigo (13). Al-Mutairi diagnosed 22% of intertrigo in a study of 437 obese patients (14). It was detected under the abdominal wall in 23% of the patients in our study. It is already an intertriginous area under the breast

and its incidence may be high. Intertrigo is most commonly seen in patients with obesity (body mass index greater than 30 kg per m^2), diabetes mellitus, or human immunodeficiency virus infection, and in bedridden patients. Obese patients sweat more abundantly due to the thick subcutaneous brown fat layers and generate more heat than people with normal body mass. This situation affects the moisture components by increasing thermal friction and prepares the ground for intertrigo (**8, 13, 15, 16**).

Folliculitis is the name given to the limited, superficial pustular inflammation of the pilosebaceous unit, which includes the hair follicle and its periphery. Hot weather and sweating, obesity, tight clothing, irritating shaving, immunodeficiency, steroid and some drug use are predisposing factors. Sometimes there are folliculitis that recurs for months or years and it is very disturbing (**17**). It is known that infections (dermatophyte infections, intertrigo, infective cellulitis, folliculitis, other fungal and bacterial infections) are more common in obesity. The excessive skin folds in obese patients and the contact of these folds with each other, their moisture, and airlessness predispose to fungal and bacterial infections. In our study, folliculitis was detected in 20% of patients.

However, this rate is relatively high compared to the literature. In a study, folliculitis was reported with a rate of 0.8% in the control group and 6% in the obese group (**18**).

CONCLUSIONS

In our study with a small number of patients, 28% of the patients had normal skin findings. In fact, if we did not include the patients with striae, 26 of the patients (43%) had other findings.

The biggest limitations of our study are that it is retrospective, the number of patients is small and there is no comparison with individuals with normal weight. Prospective and comparative studies are needed to provide more precise information about the effect of obesity on skin.

Author Contributions: NK, MY: Patient examinations, **NK, MY, SD, BÖ:** Research of the literature, Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and local approval for this study (Date: 09.11.2021 and Number: 2021/946)

REFERENCES

1. Colak B, Yormaz S, Ece İ, Acar F, Yılmaz H, Alptekin H et al. Morbid Obesity Surgery and Complications. Selcuk Medical Journal 2016; 32 (1): 19-22
2. Apovian CM. Obesity: definition, comorbidities, causes, and burden. Am J Manag Care. 2016; 22 (7 Suppl): p176-p185.
3. Matsumoto M, Ibuki A, Minematsu T, Sugama J, Horii M, Ogai K, et al. Structural changes in dermal collagen and oxidative stress levels in the skin of Japanese overweight males. Int J Cosmet Sci. 2014; 36: 477--84.
4. Aoki M, Murase T. Obesity-associated insulin resistance adversely affects skin function. PLoS One. 2019; 14 (10): e0223528.
5. Erdoğan HK, Gökdemir G, Purisa S, Altunay İK. Evaluation of Skin Findings in Adult Obese Dermatology Outpatients.Turkderm 2011; 45: 184-7
6. Nazik H, Kökçam İ, Demir B, Gül FÇ. Skin findings in overweight and obese individuals. Turkderm. 2016; 50 (2): 59-64
7. Öztürk YK, Balcı ÜG, Dosboyeva A, Mergen H, Öngel K. Frequent Problem for Obese Patients, Lymphedeme: Case Report. SDU Journal of Health Sciences Institute 2016; 7 (1): 39-40
8. Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. J Am Acad Dermatol 2007; 56 (6): 901-916.
9. Loffler H, Aramaki JU, Effendy I. The influence of body mass index on skin susceptibility to sodium lauryl sulphate. Skin Res Technol 2002; 8: 19-22.
10. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005; 141: 1527-34.
11. Rossi AB, Take Vergnanini. Cellulite: a review. J Eur Acad Dermatol Venereol 2000; 14: 251-62.
12. Hsu HS, Chen W, Chen SC, Ko FD. Colored striae in obese children and adolescents. Zhonghua Min Guo. Xiao Er Ke Yi Xue Hui Za Zhi 1996; 37: 349-52.
13. Garcia HL, Orozco TR, Gonzalez BJ, Villa AR, Dalman JJ, Ortiz PG: Dermatoses in 156 obese adults. Obes Res 1999; 7: 299--302.
14. Al-Mutairi N. Associated cutaneous diseases in obese adult patients: a prospective study from a skin referral care center. Med Princ Pract. 2011; 20 (3): 248-52.
15. Kalra MG, Higgins KE, Kinney BS. Intertrigo and secondary skin infections. Am Fam Physician 2014; 89: 569-573.
16. Seale P, Lazar MA. Brown fat in humans: turning up the heat on obesity. Diabetes. 2009; 58 (7): 1482--1484.
17. Rose. Common Bacterial Skin Infections. Ankara Med J, 2016; 16 (1): 98-114
18. Doner N, Yasar S, Ekmekci TR. Evaluation of Obesity-Associated Dermatoses in Obese and Overweight Individuals. Turkish derm 2011; 45: 146-51.

Medical Science and Discovery
ISSN: 2148-6832

Vaccination rates among adults with sickle cell disease: a single-center study from the Eastern Mediterranean region of Turkey

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ABSTRACT

Objective: Being vaccinated against encapsulated bacteria is the most efficient way to reduce painful crises and mortality in patients with sickle cell disease (SCD). Although guidelines strongly recommend vaccination, vaccination rates remain under the desired levels. In this study, we aim to determine vaccination rates and understand the reasons for non-vaccination in patients with SCD.

Material and methods: We included 76 patients with SCD in this study. We administered a questionnaire consisting of 21 questions and examined the electronic vaccination records of these patients.

Results: The vaccination rates were 36.5% for the pneumococcal vaccine, 22.4% for the Hemophilus influenza type b vaccine, and 19.7% for the meningococcal vaccine. Residence in rural areas and annual control visits were found to increase the pneumococcal vaccination rates (OR: 11.90, 95% CI: 2.549–56.107, p = 0.002 and OR: 9.08, 95% CI: 1.120–73.624, p = 0.039, respectively) and meningococcal vaccination rates (OR: 2.75, 95% CI: 1.464–5.186, p = 0.002 and OR:1.36, 95% CI: 1.159–1.610, p < 0.001, respectively). Thirty-four (44.7%) of the cases stated that their doctors did not give any information about these vaccinations.

Conclusion: Vaccination rates are low in patients with SCD. Residence in rural areas, annual control visits, educational level, and doctor recommendations affect these vaccination rates.

Keywords: Vaccination rates, sickle cell disease, reasons for non-vaccination

INTRODUCTION

Sickle cell disease (SCD) is the most common hemoglobinopathy worldwide. Impaired splenic functions, complement activation and opsonization cause increased susceptibility to infections in this disease (1). Infections, especially those caused by encapsulated microorganisms (Streptococcus pneumonia, Neisseria meningitidis, Hemophilus influenza), are the leading causes of painful crises and mortality in SCD (2).

Various studies reveal that vaccinations against encapsulated bacteria significantly decrease both infections and mortality in pediatric patients with SCD (3, 4). Current guidelines also strongly recommend vaccinations in adults with SCD (5).

However, despite the evidence regarding the importance of these vaccines for individuals with SCD, adherence to the recommended immunization schedule remains a concern around the world (6). A retrospective cohort study on a Medicaid sample shows that patients with SCD have an adherence rate of 43.4% for the 23-valent pneumococcal polysaccharide vaccine (PPSV23) (7).

Subsequent studies in the pediatric age group also state that patients with SCD still have low immunization rates (8, 9). The situation is even worse in Turkey. According to Korur et al., only 21.5% of adult patients with SCD are vaccinated against S. pneumonia (10).

Research Article

Received 06-11-2021

Accepted 20-11-2021

Available Online: 23-11-2021

Published 30-11-2021

http://dx.doi.org/10.36472/msd.v8i11.628

There are insufficient studies in the adult age group about this vital topic, and these works are only about influenza and pneumococcal vaccinations. There are no studies about other vaccinations in adult patients with SCD, especially those against N. meningitidis and H. influenza type b (**11**). Therefore, we aim to determine such vaccination rates and identify the reasons for non-vaccination in these patients.

MATERIAL and METHODS

The study comprises 76 patients with SCD admitted to the Mersin University hematology outpatient clinic between January 2020 and March 2020. The participants were asked to complete a questionnaire, which is described in Supplemental file. A hematologist was available to address their questions concerning the questionnaire. In addition to the questionnaire, the patients' hospital electronic health records regarding vaccinations were evaluated. The demographic characteristics, SCD phenotype, clinical visits per year, and replies of the patients were documented. Patients who were in vaso-occlusive crises and younger than 18 years were excluded. This study was performed in accordance with the Declaration of Helsinki, and the ethics committee of Mersin University approved this work (Approval number: 2020/13/439). Written consent was obtained from all participants.

Statistical Method: Statistical analysis was performed with SPSS Statistics 22.0 for Windows. The categorical parameters were expressed as numbers (n) and percentages (%). Whether the numerical parameters had a normal distribution was determined using a histogram, variation coefficients, and the Kolmogorov-Smirnov test. The chi-square or Fisher's exact test was used to compare the categorical variables. We performed univariate analyses to detect variables associated with the vaccination rate of each vaccine type. Parameters with a p-value of < 0.200 were included in a multivariate analysis to identify factors that were independently associated with the vaccination rates. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 76 patients were included in this study. Some characteristics of the patients are listed in Table 1. The vaccination rates were 36.5% for the pneumococcal vaccine, 22.4% for the Hib vaccine, and 19.7% for the meningococcal vaccine. The 11 (14.5%) patients with a history of splenectomy had all three vaccines. There was no difference between genders in the vaccination rates.

In total, 42 (55.3%) of the patients stated that their doctors gave information about the vaccinations. Twenty-six (61.9%) of these 42 patients had at least one dose of the pneumococcal vaccine. A total of 26 (51%) of the 51 patients living in rural areas had at least one dose of the pneumococcal vaccine. Individuals living in rural areas had a significantly higher vaccination rate compared with those who resided in urban areas (p < 0.001). Ten of the 16 patients who had educational levels of college or higher received the pneumococcal vaccine. The difference between this group and those with other educational levels was significant (p = 0.022).

While 14 (27.5%) of the 51 patients living in rural areas had the meningococcal vaccine, only 1 (4%) of the 25 patients living in urban areas had the same vaccine (p < 0.001). Twelve of the patients who received vaccination recommendations from their doctors had the meningococcal vaccine. The difference between this group and those who were not recommended vaccination was significant (p = 0.007). No significant difference was noticed between educational levels in meningococcal vaccination.

Residence in rural areas and doctors' recommendations did not significantly differentiate Hib vaccination. The only significant point in terms of Hib vaccination was the educational level. Seven of the 16 patients who had an educational level of college or higher received the Hib vaccine (p = 0.049).

Findings showed that as the number of people living in the same house decreased and the number of annual control visits increased, the rates of pneumococcal and meningococcal vaccination increased significantly (p< 0.001), but the change in the Hib vaccination rate was insignificant. Variables that significantly affected the vaccination rates in the univariate analyses were then included in a multivariate analysis, and the results are summarized in **Table 2**.

Regarding the reasons for not being vaccinated against S. pneumonia, 34 (44.7%) of the patients answered, 'I did not know its necessity,' which was the most common reason (**Figure 1**). **Figures 2** and **3** show the responses of the patients who did not have the Hib and meningococcal vaccines, respectively.

Table 1: Some characteristics of the patients (N = 76)

Characteristics	Value
Gender, n (%)	
Female	44 (57.9%)
Male	32 (42.1%)
Age, yr, mean (range)	34.3 (18–58)
SCD phenotype, n (%)	
HbSS	67 (88.1%)
HbSß	9 (11.9%)
Educational status, n (%)	
Elementary school graduate	29 (38.2%)
Middle school graduate	9 (11.8%)
High school graduate	22 (28.9%)
College or higher graduate	16 (21.1%)
Living area of the patient	
Urban area	25 (32.9%)
Rural area	51 (67.1%)
Splenectomy	11 (14.5%)
Number of people living in the same house	
1	1 (1.3%)
2	8 (10.5%)
3	15 (19.7%)
4	22 (28.9%)
5	22 (28.9%)
6	7 (9.2%)
7	1 (1.3%)
Control visits per year	
0	12 (15.8%)
1–3	31 (40.8%)
4–7	22 (28.9%)
8–12	11 (14.5%)
Vaccination rates	
S. pneumonia	28 (36.8%)
N. meningitidis	15 (19.7%)
H. influenza type b	17 (22.4%)

http://dx.doi.org/10.36472/msd.v8i11.628

Table 2: Significant factors affecting vaccination rates (multivariate analyses)

	OR	%95 CI	p-value
Pneumococcal vaccination rate			
Residence in rural area	11.90	2.549–56.107	0.002
Doctor recommendation	36.23	2.690–488.270	0.007
Annual control visits	2.75	1.464–5.186	0.002
Meningococcal vaccination rate			
Residence in rural area	9.08	1.120–73.624	0.039
Annual control visits	1.36	1.159–1.610	< 0.001
***H. influenza* vaccination rate**			
Educational level of college or higher	3.88	1.173–12.893	0.026

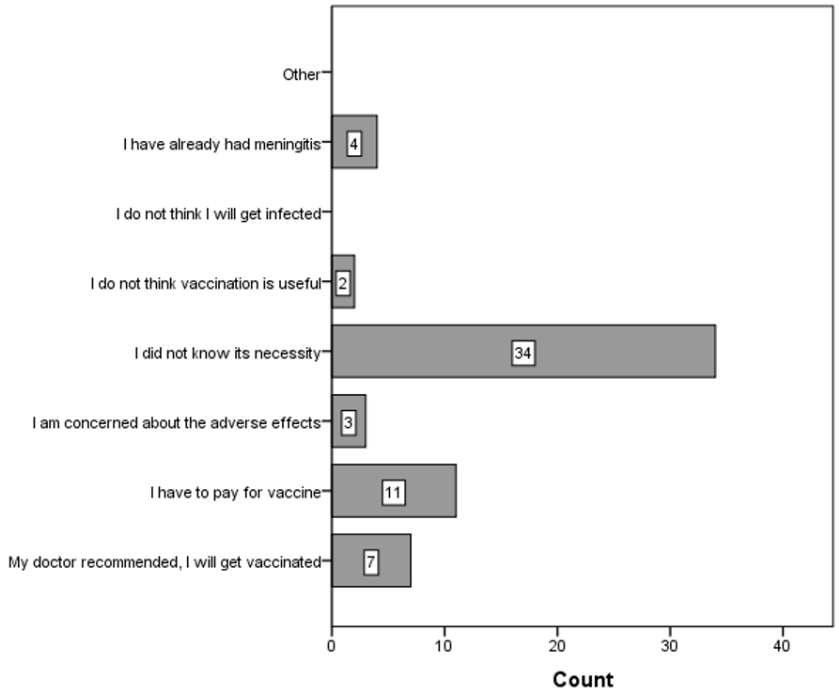

Figure 1: Reasons for not being vaccinated against S. pneumonia

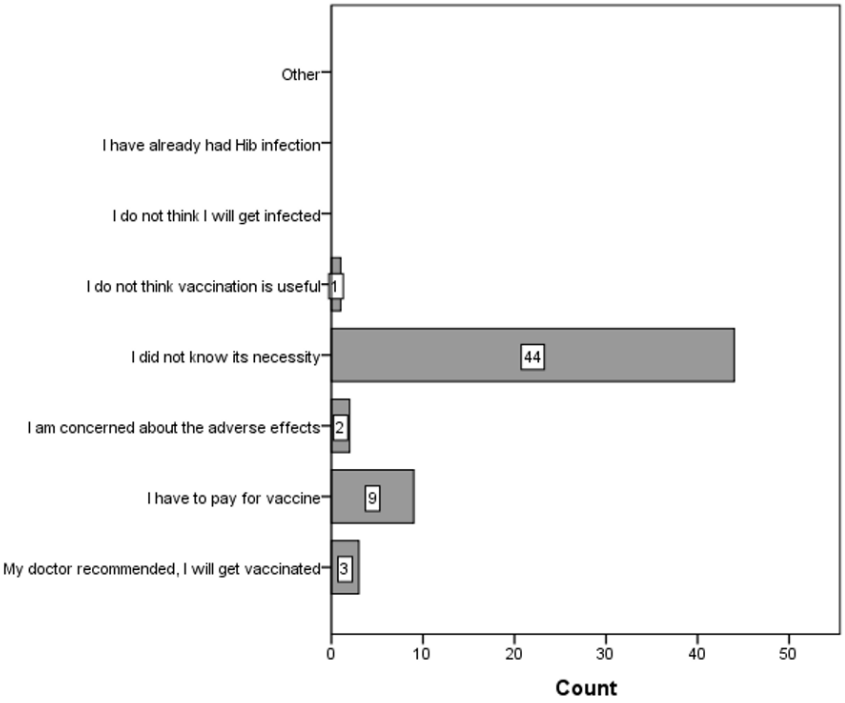

Figure 2: Reasons for not being vaccinated against H. Influenza type b

DISCUSSION

According to the National Institute of Health (NIH) expert panel report in 2014, all individuals with SCD should be immunized as recommended by the Advisory Committee on Immunization Practices (ACIP) (**5**). Adults aged ⩾19 years with SCD who have not received the 13-valent pneumococcal conjugate vaccine (PCV13) or 23-valent pneumococcal polysaccharide vaccine (PPSV23) should receive one dose of PCV13 first, followed by a dose of PPSV23 at least eight weeks later. A second PPSV23 dose five years after the first PPSV23 dose is recommended. One dose of the Hib vaccine (if the patient has not received it) and the meningococcal vaccine with five-year boosters are also strongly recommended. Hepatitis B and yearly influenza vaccinations are likewise advocated. Studies show that pneumococcal infections are the leading cause of mortality and morbidity in patients with SCD; correspondingly, vaccination is effective in these patients (**12**). Therefore, an active immunization schedule should be maintained throughout life, beginning in infancy. In Turkey, pneumococcal vaccination was added to the routine childhood immunization schedule in 2009. In contrast, H. influenza and meningococcal vaccines are not part of the routine schedule yet.

This study demonstrates poor vaccination rates against encapsulated bacteria. According to Infanti et al., even in countries whose routine immunization schedules cover all three encapsulated bacteria, the pneumococcal and meningococcal vaccination rates are only 77% and 25%, respectively (**13**). A study on adult and pediatric patients in the United Kingdom revealed that only 21% of adult patients and 72% of pediatric patients are vaccinated against S. pneumonia (**14**). Nero et al. showed that children with SCD have a vaccination rate of 75% against S. pneumonia, and patients with SCD have higher adherence to vaccination than the normal pediatric age population (**8**). A recent pediatric study showed that only about 50% of patients with SCD had received both the first dose and boosters of the pneumococcal vaccine (**9**). According to another comprehensive study, the total dose vaccination rate against S. pneumonia in children is merely around 35%. Existing studies about this issue mainly include patients in the pediatric age group. There are very few works regarding vaccination profiles in the adult age group. Therefore, vaccination rates among adult patients with SCD are poor, as our study also verifies. A previous work from Turkey stated that only 21.5% of adult patients with SCD are vaccinated against S. pneumonia (**9**). The numbers are even worse for Hib and N. meningitidis vaccinations. Our results seem similar to those from a few published studies, including those on adults, regarding pneumococcal vaccination rates. However, we could not find studies about H. influenza or N. meningitidis vaccination rates in adult patients with SCD. Therefore, this study may be the first to show that vaccination rates against these two bacteria are worse than pneumococcal vaccination rates.

A survey was prepared to understand precisely the reasons for non-vaccination. The answers of the unvaccinated patients indicate massive problems in informing patients about the importance of being vaccinated. The number of patients who did not receive vaccination despite their doctors' recommendations is relatively low. Thus, a significant factor behind the low vaccination rates in these patients is lack of information and recommendation from health care providers. Therefore, ways should be established to increase these patients' awareness of vaccination. Studies have been performed to address this issue. Korur et al. evaluated the effectiveness of electronic medical record (EMR) systems, which inform health care providers about the immunization status of patients and upcoming vaccination dates (**10**). In this study, the influenza vaccination rates increased to 49.2% from 23.7%, and the pneumococcal vaccination rates became 50.8% from 20.3% after the use of an alert intervention EMR system. In some studies, the use of a database to send reminders about high-risk pediatric patients, followed by recall letters for unvaccinated patients, showed increases in both influenza and pneumococcal vaccination rates (**15, 16**).

According to the patients' answers, another minor problem is their belief that they will have to pay for these vaccines. The general social insurance in Turkey reimburses influenza and pneumococcal vaccines for high-risk patients, whereas meningococcal and H. influenza vaccines are not repaid. This problem should be explained to these patients.

Primary care providers are a potential barrier to vaccination adherence. This may include lack of education about SCD. New studies about the knowledge of primary care providers regarding this high-risk patient population should thus be designed. In addition to lacking knowledge, primary care physicians may not be willing to follow up with these patients and refer them to tertiary care hematology centers. Bundy et al. observed an increased compliance rate for the influenza vaccine in SCD patients who visited their hematologists two or more times per year than those without a hematologist visit (**17**). In our study, the multivariate analysis showed that the number of annual control visits is an independent factor that increases pneumococcal and meningococcal vaccination rates (**Table 2**).

In this study, the main problem identified is that most patients do not have sufficient information about vaccination. In our opinion, the first problem to address should be to increase the knowledge of patients about vaccination. This can be done in three ways. First, cooperation between hematologists and primary care clinicians is essential. Since most immunizations are provided at primary care visits, initiatives should be made to increase the awareness of patients in the primary care setting. Second, time should be dedicated to educating these patients and their families about vaccination during their hematology visits. Third, vaccination schedules and notifications about upcoming vaccination dates should be integrated into medical record systems. In this manner, many patients with SCD can be referred to their primary care providers to receive the recommended immunizations.

One of the main limitations of this study is the relatively small sample size (this study is a single-center study). Moreover, the vaccination rates in this work were based on receiving at least one dose of a vaccine. Thus, the numbers do not reflect the completion of the vaccination course.

CONCLUSIONS

In conclusion, patients with SCD are at increased risks of infection and mortality due to encapsulated organisms. Hence, these high-risk patients must adhere to the recommended immunization schedule. However, vaccination

rates are evidently low in patients with SCD, and lack of information about vaccination is a significant factor. Institutions should then identify the barriers to vaccination and strive to solve them.

Author Contributions: KBK, CC, ESH, AT: Research of the literature, Patient examinations, **KBK:** Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and local approval was obtained from the local ethical commission.

REFERENCES

1. Tamouza R, Neonato MG, Busson M, Marzais F, Girot R, Labie D, et al. Infectious complications in sickle cell disease are influenced by HLA class II alleles. Hum Immunol. 2002;63(3):194-9.
2. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. Int J Infect Dis. 2010;14(1):e2-e12.
3. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. Blood. 2004;103(11):4023-7.
4. John AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR. Prevention of pneumococcal infection in children with homozygous sickle cell disease. Br Med J (Clin Res Ed). 1984;288(6430):1567-70.
5. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. Jama. 2014;312(10):1033-48.
6. Walsh KE, Cutrona SL, Kavanagh PL, Crosby LE, Malone C, Lobner K, et al. Medication adherence among pediatric patients with sickle cell disease: a systematic review. Pediatrics. 2014;134(6):1175-83.
7. Beverung LM, Brousseau D, Hoffmann RG, Yan K, Panepinto JA. Ambulatory quality indicators to prevent infection in sickle cell disease. Am J Hematol. 2014;89(3):256-60.
8. Nero AC, Akuete K, Leasure Reeves S, Dombkowski KJ. Pneumococcal vaccination rates in children with sickle cell disease. J Public Health Manag Pract. 2014;20(6):587-90.
9. Wagner AL, Shrivastwa N, Potter RC, Lyon-Callo SK, Boulton ML. Pneumococcal and Meningococcal Vaccination among Michigan Children with Sickle Cell Disease. J Pediatr. 2018;196:223-9.
10. Korur A, Asma S, Gereklioglu C, Solmaz S, Boga C, Ozsahin AK, et al. Significance of electronic health records: A comparative study of vaccination rates in patients with sickle cell disease. Pak J Med Sci. 2017;33(3):549-53.
11. Fujino T, Goyama S, Sugiura Y, Inoue D, Asada S, Yamasaki S, et al. Mutant ASXL1 induces age-related expansion of phenotypic hematopoietic stem cells through activation of Akt/mTOR pathway. Nature Communications. 2021;12(1):1826.
12. Halasa NB, Shankar SM, Talbot TR, Arbogast PG, Mitchel EF, Wang WC, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis. 2007;44(11):1428-33.
13. Infanti LM, Elder JJ, Franco K, Simms S, Statler VA, Raj A. Immunization Adherence in Children With Sickle Cell Disease: A Single-Institution Experience. J Pediatr Pharmacol Ther. 2020;25(1):39-46.
14. Howard-Jones M, Randall L, Bailey-Squire B, Clayton J, Jackson N. An audit of immunisation status of sickle cell patients in Coventry, UK. J Clin Pathol. 2009;62(1):42-5.
15. Sobota AE, Kavanagh PL, Adams WG, McClure E, Farrell D, Sprinz PG. Improvement in influenza vaccination rates in a pediatric sickle cell disease clinic. Pediatric Blood & Cancer. 2015;62(4):654-7.
16. Daley MF, Barrow J, Pearson K, Crane LA, Gao D, Stevenson JM, et al. Identification and recall of children with chronic medical conditions for influenza vaccination. Pediatrics. 2004;113(1 Pt 1):e26-33.
17. Bundy DG, Muschelli J, Clemens GD, Strouse JJ, Thompson RE, Casella JF, et al. Preventive Care Delivery to Young Children With Sickle Cell Disease. Journal of pediatric hematology/oncology. 2016;38(4):294-300.

MSD

Medical Science and Discovery
ISSN: 2148-6832

Predictive value of the aspartate aminotransferase to platelet ratio index and aspartate aminotransferase to alanine aminotransferase ratio in early diagnosis of intrahepatic cholestasis in pregnancy

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ABSTRACT

Objective: We aimed to investigate the predictive value of the first-trimester aspartate aminotransferase/platelet count ratio index (APRI) and aspartate aminotransferase/alanine aminotransferase ratio for intrahepatic cholestasis in pregnancy (ICP).

Material and Methods: The clinical data of patients who admitted to the Obstetrics Department of Umraniye Training and Research Hospital, between 2015-2020 were analyzed retrospectively. The study group consisted of 44 patients with ICP and the control group consisted of randomly selected 92 healthy pregnant women.

Results: The two groups were similar in terms of age, BMI, first and third-trimester platelet count and third-trimester hemoglobin level. Patients with ICP had a significantly higher first-trimester APRI and a lower first trimester AST/ALT ratio than the healthy controls ($p < 0.001$, $p = 0.001$, respectively). According to the ROC analysis, the optimal cut-off value of the APRI to predict ICP was 0.191, with the sensitivity of 0.66 and specificity of 0.66 (AUC: 0,727), and the optimal cut-off value for AST/ALT ratio was 1.07, with the sensitivity of 0.64, and specificity of 0.62 (AUC: 0,681).

Conclusion: The first-trimester APRI score and AST/ALT ratio is an easy, inexpensive, and non-invasive tool that may be useful in predicting ICP early.

Keywords: Cholestasis, pregnancy, aspartate aminotransferases, alanine transaminase, blood platelets

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic disease that occurs during the second or third trimester of pregnancy, characterized by increased serum aminotransferase activity and high bile acid levels with pruritus. The reported incidence of ICP varies between countries and populations in a range of 0.2 – 22% (**1**). Although it is thought that genetic factors, mutations in hepatocellular phospholipid transporter, hormonal factors, familial clustering, ethnic and geographical variations may contribute to the pathogenesis, the etiology of ICP is not fully understood yet. ICP, which usually resolves spontaneously a few weeks after birth, increases the risk of meconium-stained amniotic fluid, fetal distress, preterm labor and fetal loss during the pregnancy (**1**).

Recently, Aspartate aminotransferase (AST) - platelet ratio index (APRI) has been used in pediatrics to diagnose cholestatic liver diseases and fibrosis. According to these studies, APRI score can be a reliable and non-invasive marker in the development of paranteral nutrition associated cholestasis (**2**) and distinguishing mild and advanced fibrosis in patients with cholestatic liver disease (**3**) or in the evaluation of graft fibrosis after liver transplantation (**4**). Also, Aspartate aminotransferase - alanine aminotransferase ratio index (AST/ALT) has been investigated as a marker of cirrhosis in patients with primary biliary cirrhosis, and it has been reported to have clinical value in the diagnosis of cirrhosis (**5**). In obstetric practice, there is no screening test yet to provide early prediction of ICP development in daily use. Whether APRI and AST/ALT ratio are also reliable predictors for ICP is a question. The aim of this study is to investigate the use of APRI and AST/ALT ratio in early diagnosis of ICP.

Research Article

Received 01-11-2021

Accepted 23-11-2021

Available Online: 24-11-2021

Published 30-11-2021

http://dx.doi.org/10.36472/msd.v8i11.623

MATERIAL and METHODS

The clinical data of patients who were admitted to the Gynecology and Obstetrics Department of Umraniye Training and Research Hospital, Istanbul, Turkey between 2015-2020 with a diagnosis of ICP between 2015-2020 were scanned retrospectively. The study group consisted of 44 patients with ICP, whose pregnancy follow-up and delivery were in our hospital. In third trimester, patients with generalized itching without a dermatopathological pathology, elevated serum AST, ALT or fasting bile acid, normal hepatobiliary ultrasonographic imaging findings and negative serological test results for hepatitis A, B and C were diagnosed with ICP. Patients with multiple pregnancies, dermatologic disorders, preeclampsia or chronic hypertension, gestational or pregestational diabetes mellutis, intrauterine growth retardation, placental pathologies, chronic systemic or autoimmune or endocrinological diseases, liver diseases, hematological or infectious diseases, blood product transfusion or steroid use for the last year, were excluded from the study. The control group consisted of 92 randomly selected healthy pregnant women who did not have any pregestational or gestational disease, whose pregnancy follow-ups were made in our hospital, and who gave birth in our hospital in the same period as the patients in the study group.

Age, gravida, parity, living, miscarriage, body mass index (BMI), AST, ALT, and PLT levels in the first and third trimesters, hemogram, and fasting bile acid levels in the third trimester were recorded for both groups.

Complete blood count of the patients was studied in the automatic hematology analyzer Mindray BC6800 machine, and AST, ALT and fasting bile acid were studied in the Roche Cobas 8000 device in accordance with the recommendations of the manufacturer.

First-trimester APRI were calculated using the following formula: serum AST (IU/L)/upper limit of normal x 100/platelet count (109 /L), taking the upper limit of normal to be 34 IU/L.

First trimester AST/ALT ratios were calculated using the following formula: serum AST (IU/L)/ALT (IU/L).

According to the system used in our hospital's laboratory upper limit of normal for AST is 34 U/L, 55U/L for ALT, and 10 µmol/L for fasting bile acid.

Statistical Package for the Social Sciences (SPSS) Version 25.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses in this study. Descriptive statistical methods (mean, standard deviation, frequency) were used while evaluating data of the study. The distribution of data was tested with the Kolmogorov Smirnov test. Parametric Independent two samples t-test was used for normally distributed data and non-parametric The Mann Whitney U-test was used for data that did not show normal distribution. The level of significance was evaluated at $p < 0.05$ levels for all values. A receiver operating characteristic (ROC) analysis was performed to determine the cut-off value for APRI and AST/ALT ratio for the prediction of ICP.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; APRI: aspartate aminotransferases to platelet ratio index; ROC: receiver-operating characteristic; AUROC: area under receiver-operating characteristic; PAPP-A: pregnancy associated plasma protein A; MoM: multiple of median; β-hCG: β-human chorionic gonadotropin.

RESULTS

The baseline characteristics of the ICP group and the control group were compared. Patients with ICP did not differ significantly from controls in terms of mean age, BMI, gravida, parity, living, miscarriage, first and third trimester platelet count and third trimester hemoglobin level. First and third trimester ALT and AST levels of patients with ICP were significantly higher than controls (for all four $p < 0.001$) (**Table 1**).

Patients with ICP had a significantly higher first-trimester APRI and a lower first trimester AST/ALT ratio than healthy controls ($p < 0.001$, $p = 0.001$, respectively) (Table2). According to the ROC analysis, the optimal cut-off value of the APRI to predict ICP was 0.191, with the sensitivity of 0.66 and specificity of 0.66 (AUC: 0,727), and the optimal cut-off value for AST/ALT ratio was 1.07, with the sensitivity of 0.64, and specificity of 0.62 (AUC: 0,681) (**Fig 1 and 2**).

Table 1. Baseline characteristics of patients

	Without cholestasis (n=92)		With cholestasis (n=44)		
Variables	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p-value
Age*	27,2 ± 5,5	27,5 (18-38)	28,6 ± 5	29 (20-42)	0,139
BMI**	23,7 ± 1,4	23,5 (19,5-26,5)	23,8 ± 1,6	24 (19-27)	0,281
Gravida**	2,5 ± 1,5	2 (1-7)	2,2 ± 1,2	2 (1-5)	0,145
Parity**	1,2 ± 1,1	1 (0-4)	0,9 ± 1,1	1 (0-4)	0,054
Living**	1,2 ± 1,1	1 (0-4)	0,9 ± 1,1	1 (0-4)	0,062
Miscarriage**	0,3 ± 0,7	0 (0-4)	0,3 ± 0,5	0 (0-2)	0,944
1st ALT (IU/L)**	13,1 ± 5,2	12,5 (6-35)	24,1 ± 14,8	21 (6-90)	0,000
1st AST (IU/L)**	14,8 ± 3,2	14 (8-31)	21,5 ± 9,5	18 (10-48)	0,000
1st PLT (103/uL)*	258,5 ± 52	249 (174-419)	249,1 ± 58,5	237,5 (143-373)	0,342
3rd ALT (IU/L)**	11,9 ± 8,3	10 (5-77)	115,4 ± 86,9	101,5 (10-478)	0,000
3rd AST (IU/L)**	19,4 ± 6,1	19 (10-50)	79,3 ± 53,4	68 (15-288)	0,000
3rd Hb (g/dL)*	11,4 ± 1,6	11,6 (7,5-14,9)	11,3 ± 1,3	11,5 (8-13,6)	0,636
3rd PLT(103/uL)**	236,2 ± 57,3	229 (110-389)	240,2 ± 64,1	236 (129-398)	0,796
Fasting bile acid (µmol/L)	-	-	30,3 ± 34,5	17,5 (1,4-137,5)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase, Hb: hemoglobin, PLT: Platelet, SD: standard deviation. *Independent two samples t-test, ** Mann-Whitney U-test.

http://dx.doi.org/10.36472/msd.v8i11.623

Table 2. APRI and AST/ALT ratio by patient groups

Variables	Without cholestasis (n=92)		With cholestasis (n=44)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p-value**
APRI	0,17 ± 0,05	0,18(0,07-0,38)	0,27 ± 0,13	0,24(0,1-0,63)	**0,000**
AST/ALT ratio	1,26 ± 0,42	1,2(0,47-2,33)	1,03 ± 0,44	0,91(0,41-2,5)	**0,001**

**Mann Whitney U test

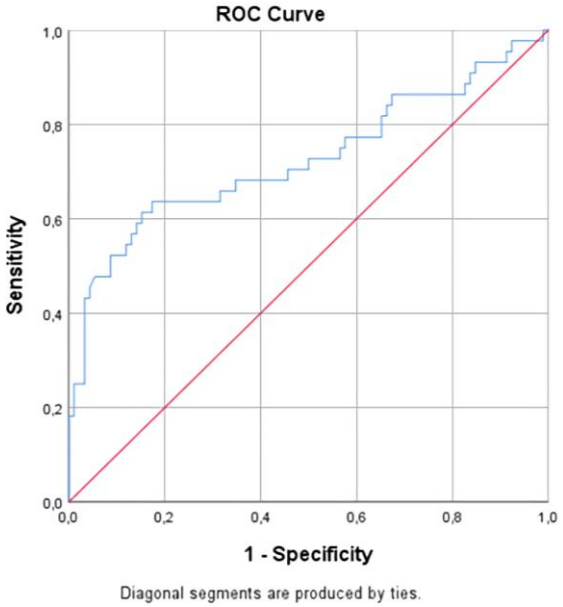

Figure 1. Receiver operating characteristic curve analysis for first trimester APRI

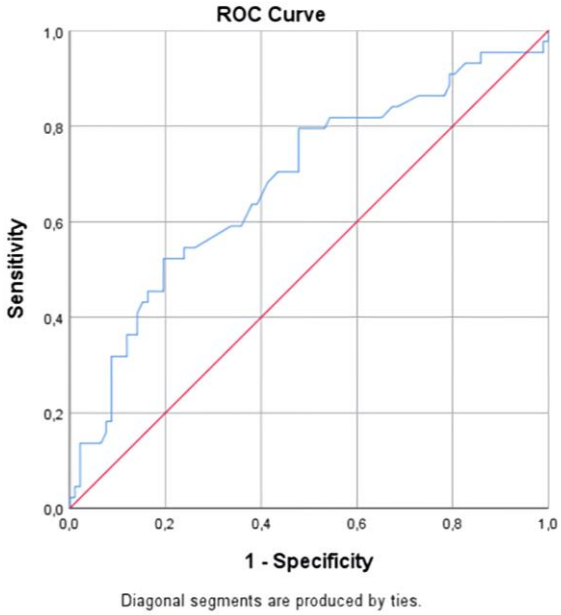

Figure 2. Receiver operating characteristic curve analysis for first trimester AST/ALT ratio

DISCUSSION

This study revealed that the first-trimester high APRI and low AST/ALT ratio may be associated with the development of ICP in subsequent gestational weeks. In the literature, studies about ICP have generally focused on fetal and maternal poor outcomes in the third trimester, and there are only a few reported studies for early prediction of ICP in the first trimester.

As a very recent study, in 2021, Turhan et al. found Lysyl oxidase like protein 2 (LOXL-2) measured in maternal serum was significantly higher in women with ICP compared to the healthy control group. They suggested that LOXL-2 could be used in the prediction of ICP in early pregnancy, although it was investigated in the third trimester (**6**). The most studied other biomarkers in the early prediction of ICP are serum markers of Down syndrome screening tests. According to one study, the decrease in first trimester maternal serum

pregnancy associated plasma protein A (PAPP-A) multiple of median (MoM) indicates an increased risk of developing ICP, while changes in the first trimester free β-human chorionic gonadotropin (β-hCG) or the second trimester total β-hCG, estriol or α- fetoprotein was not enough to predict (7). Similarly, another study published in 2015 showed that a decrease in the first trimester PAPP-A MoM, increases the risk of developing ICP (8).

Unlike these two studies; in another study in which the first trimester PAPP-A MoM levels and pregnancy complications were examined in ICP, no significant difference was found between the maternal serum PAPP-A MoM levels of the ICP group and the healthy control group (9). In addition to these confusing results, when we consider that not all pregnant women have Down syndrome screening test in the first trimester, the role of PAPP-A in predicting ICP remains limited.

The APRI has been described as a non-invasive index of hepatic fibrosis and cirrhosis in patients with chronic hepatitis C (10), and was later used in the evaluation of long term graft fibrosis in pediatric liver transplant patients (4). In a different study conducted on pregnant women with chronic liver disease, APRI was found to be significantly higher in those with cirrhosis than those without cirrhosis, and it was stated that APRI could be used in predicting of live birth in patients with chronic liver disease (11). Also, APRI was investigated in HELLP syndrome by Şaşmaz et al. and it was revealed that APRI is a stronger marker than AST in predicting HELLP syndrome (12). In 2020, Tolunay et al. investigated the relationship between the APRI and ICP. Although the formulation of the APRI is not clearly stated, the first tirmester APRI of patients with ICP was significantly higher than controls ($p < 0.001$), and the optimal cut-off value of the APRI to predict ICP was determined to be 0.57 (13). Similar to this study, we found that the first trimester APRI of patients with ICP was significantly higher than healthy controls in our study, and and the optimal cut-off value of the APRI to predict ICP was found to be 0.191. With the study of Tolunay et al. (13), we think that the difference in the optimal cut-off values for APRI is due to the calculation of APRI with different formulas. In this study, the first-trimester APRI was calculated using the following formula based on previous reference studies (4, 9, 13) : serum AST (IU/L)/upper limit of normal x 100/platelet count (10^9 /L), taking the upper limit of normal to be 34 IU/L.

It has been shown that the AST/ALT ratio is a non-invasive, reliable maker that can be used to detect the development of secondary liver cirrhosis in patients with alcohol abuse (15), chronic hepatitis C (16), and patients with primary sclerosing cholangitis (17). High AST/ALT ratio was found to be a reliable indicator of poor outcomes and liver cirrhosis in these patients. In the light of these informations, we investigated the first trimester AST/ALT ratio in addition to the APRI in terms of predicting ICP in early pregnancy. According to this study, patients with ICP had a significantly lower first trimester AST/ALT ratio than healthy controls.

Many pregnant women living in underdeveloped or developing countries, with low socioeconomic status or living in rural areas cannot receive regular pregnancy follow-up services, and most of them receive primary health care only from family health centers until delivery. We think that the APRI score and AST/ALT ratio obtained by simple and inexpensive laboratory tests even by family physicians in the early weeks of pregnancy can be used in the early detection of pregnant women at risk for ICP development. Thus, these pregnant women will be informed about ICP and they will be directed to obstetric centers for regular pregnancy follow-up.

CONCLUSIONS

Today, the prevention of pregnancy-related complications is considered as important as much as the management of complications and treatments. Early prediction of ICP development, which increases the risk of meconium-stained amniotic fluid, fetal distress, preterm birth and neonatal intensive care unit admission, may prevent the development of serious perinatal complications. In this context, we investigated the relationship between first trimester APRI and AST/ALT ratio with early ICP prediction. According to the author's knowledge, this study is considered to be the first study investigating the relationship between the first trimester AST/ALT ratio and ICP. However, study has retrospective nature, being single center and limited number of patients are the limitations of the study.

In conclusion, the first trimester APRI score and AST/ALT ratio is an easy, inexpensive and non-invasive tool that can be useful in early predicting ICP. We believe that the results of this study should be supported by large number of patients and multi-center prospective studies.

Author Contributions: İK: Research of the literature, Patient examinations, **İK:** Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and local approval was obtained from the local ethical commission.

REFERENCES

1. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014 Jul;124(1):120–33.

2. Hwang JH, Chung ML. Predictive value of the aspartate aminotransferase to platelet ratio index for parenteral nutrition associated cholestasis in extremely low birth weight infants. BMC Pediatr. 2019 Apr 24;19(1):126.

3. Ünlüsoy Aksu A, Sarı S, Yılmaz G, Eğritaş Gürkan Ö, Demirtaş Z, Dalgıç B. Aspartate aminotransferase-to-platelet ratio index in children with cholestatic liver diseases to assess liver fibrosis. Turk J Pediatr. 2015 Oct;57(5):492–7.

4. D'Souza RS, Neves Souza L, Isted A, Fitzpatrick E, Vimalesvaran S, Cotoi C, et al. AST-to-platelet ratio index in non-invasive assessment of long-term graft fibrosis following pediatric liver transplantation. Pediatr Transplant. 2016 Mar;20(2):222–6.

5. Nyblom H, Björnsson E, Simrén M, Aldenborg F, Almer S, Olsson R. The AST/ALT ratio as an indicator of cirrhosis in patients with PBC. Liver Int Off J Int Assoc Study Liver. 2006 Sep;26(7):840–5.

6. Turhan U, Şahin B, Dağ İ. Lysyl oxidase like protein-2 (LOXL-2); a novel marker for prediction of intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med. 2021 Jul 18;34(14):2363–8.

7. Tayyar AT, Tayyar A, Atakul T, Yayla CA, Kilicci C, Eser A, et al. Could first- and second-trimester biochemical markers for Down syndrome have a role in predicting intrahepatic cholestasis of pregnancy? Arch Med Sci AMS. 2018 Jun;14(4):846–50.

8. Hançerlioğullari N, Aktulay A, Engin-Üstün Y, Ozkan MŞ, Oksuzoglu A, Danişman N. Pregnancy-associated plasma protein a levels are decreased in obstetric cholestasis. Clin Exp Obstet Gynecol. 2015;42(5):617–8.

9. Aksan Desteli G, Sahin-Uysal N, Cok T, Gulumser C, Kalayci H, Yanik FF. First trimester maternal serum PAPP-A levels and associated pregnancy complications in intrahepatic cholestasis of pregnancy. Clin Exp Obstet Gynecol. 2016;43(5):673–7.

10. Wai C-T, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatol Baltim Md. 2003 Aug;38(2):518–26.

11. Gonsalkorala ES, Cannon MD, Lim TY, Penna L, Willliamson C, Heneghan MA. Non-Invasive Markers (ALBI and APRI) Predict Pregnancy Outcomes in Women With Chronic Liver Disease. Am J Gastroenterol. 2019 Feb;114(2):267–75.

12. Şaşmaz Mİ, Ayvaz MA, Dülger AC, Kuday Kaykısız EK, Güven R. Aspartate-aminotransferase to platelet ratio index score for predicting HELLP syndrome. Am J Emerg Med. 2020 Mar;38(3):459–62.

13. Tolunay HE, Kahraman NÇ, Varlı EN, Ergani SY, Obut M, Çelen Ş, et al. First-trimester aspartate aminotransferase to platelet ratio index in predicting intrahepatic cholestasis in pregnancy and its relationship with bile acids: A pilot study. Eur J Obstet Gynecol Reprod Biol. 2021 Jan;256:114–7.

14. Huang C, Seah JJ, Tan CK, Kam JW, Tan J, Teo EK, et al. Modified AST to platelet ratio index improves APRI and better predicts advanced fibrosis and liver cirrhosis in patients with non-alcoholic fatty liver disease. Clin Res Hepatol Gastroenterol. 2020 Nov 29;101528.

15. Nyblom H, Berggren U, Balldin J, Olsson R. High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol Alcohol Oxf Oxfs. 2004 Aug;39(4):336–9.

16. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol. 1998 Jan;93(1):44–8.

17. Nyblom H, Nordlinder H, Olsson R. High aspartate to alanine aminotransferase ratio is an indicator of cirrhosis and poor outcome in patients with primary sclerosing cholangitis. Liver Int Off J Int Assoc Study Liver. 2007 Jun;27(5):694–9.

MSD

Medical Science and Discovery
ISSN: 2148-6832

The relationship between hopelessness and perceived social support levels of parents with children with congenital heart disease

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ABSTRACT

Objective: This study was conducted to evaluate the relationship between hopelessness and perceived social support levels of parents with children with congenital heart disease (CHD).

Material and Methods: This cross-sectional study was conducted with parents of children who underwent surgery for CHD, and data were collected from 100 parents who agreed to participate in the study. A descriptive information form for the sociodemographic characteristics of the parents, "Beck Hopelessness Scale (BHS)" and "Multidimensional Scale of Perceived Social Support (MSPSS)" were used to collect the data. Data were analysed using descriptive statistics and Spearman's correlation tests.

Results: The mean score of the hopelessness level of the parents participating in the study was 6.15±4.23, and the mean perceived general social support score was 69.55±15.47. There was a significant negative correlation between the hopelessness levels of mothers and social support (SS) received from the family, from significant others, and general SS scores. There was a significant positive correlation between the hopelessness levels of the mothers and the SS level received from the family ($p<0.05$).

Conclusion: In this study, the parents of children with CHD have low levels of hopelessness and perceived SS levels are high. Moreover, the relationship between hopelessness and perceived SS levels varies according to the sex of the parents. In our study, the SS level of mothers had a higher effect on the hopelessness level. It is recommended that the SS levels of the parents of children with CHD should be increased to help them cope with hopelessness.

Key words: Congenital abnormalities; hope; social support; parents

INTRODUCTION

Congenital heart diseases (CHD) are a common type of congenital anomaly that can be seen in 1–8 out of every 100 live births and is responsible for ~30%–50% of birth defects in infants and early childhood (1-2). Mortality and morbidity rates in CHD are related to the type of disease. Cyanotic CHD has a more critical course (3). Babies with critical health conditions can start medical treatment and undergo surgery within one year after birth (4).

Having a child with CHD can be very stressful for parents (5). When parents learn that they will have a baby, they can have high expectations and hope. Despite technological advances, many families of babies with CHD are unaware of the diagnosis throughout pregnancy. Families can face the fact that their baby is born with a potentially life-threatening situation a few hours, days, or weeks after a baby's birth celebration. The effect of the child's illness on the parent changes as per the life-threatening nature of the disease (6). Parents are faced with short- or long-term psychological mood changes with the start of diagnosis and treatment procedures. Hopelessness is one of them (7). Hopelessness is defined as a set of cognitive schemas that contain negative expectations about the individual and his/her future life (8). Hopelessness experienced by the family negatively affects individuals' compliance with treatment, their efforts, motivation and coping mechanisms (9).

Case Report Article

Received 08-11-2021

Accepted 25-11-2021

Available Online: 26-11-2021

Published 30-11-2021

Social support (SS) those individuals receive from their relatives is important in developing coping mechanisms for hopelessness. Individuals are required to get SS from family, friends, people in similar situations or significant others such that they do not feel lonely. SS can help parents not feel lonely and get emotional support. SS is the sum of the material and spiritual aids that are provided by relatives and friends to increase the resilience of the individual to stress, to protect the mental/physical well-being and to prevent the development of psychopathology against the problem (**10**). The lack of adequate SS mechanisms in parents with children with CHD may increase the risk of developing psychological disorders (**7**).

The relationship between the level of hopelessness and perceived SS on different populations has been investigated in the national and international literature (**8, 11-13**). Generally, studies conducted on parents with children with CHD examine the relationship between SS level and quality of life and stress level (**14, 15, 16**). There are no published studies examining the relationship between hopelessness and perceived SS level in parents with children with CHD. Therefore, this study was conducted to evaluate the relationship between hopelessness and perceived SS levels of families with children with CHD.

Study Question

1. Is there a relationship between the hopelessness level and the perceived SS level in parents who have a child with CHD?

MATERIAL and METHODS

This study is a cross-sectional research. The study was conducted with families of children aged 0–6 who were admitted to the cardiovascular surgery department (CVD) of a university hospital in Izmir, diagnosed with CHD and underwent surgery. The population of the study comprised parents of children who were admitted to the CVD because of CHD and underwent surgery. The sample of the study comprised 96 parents (mothers or fathers) determined as per a priori power analysis. The sample size was determined to be 100 for convenience in statistical evaluation. Parents who volunteered to participate in the research, over the age of 18, healthy mental status, without vision, hearing or speech problems, speaks Turkish language, with children aged 0–6 years who underwent surgery for congenital heart disease were included in the study.

An introductory information form evaluating the socio-demographic characteristics of the parents and their children, a questionnaire form comprising the MSPSS and the BHS were used to collect the data. Data were collected between August and December 2015.

Descriptive Information Form: The form comprised three closed-ended and two open-ended questions about sociodemographic information of the child with CHD and the parents, prepared by the researchers in line with the literature. The form included the parents' sex, age, educational status, as well as the age, sex and diagnosis of the child.

Beck Hopelessness Scale (BHS): The scale was developed by Beck et al. (**17**). Turkish validity was made by Seber et al. (**18**), and the scale was adapted to our country after being examined with a larger sample by Durak & Palabıyıkoglu (**19**). The scale comprises 20 items. According to the answer key, 11 of the items should be answered 'yes' and 9 should be answered 'no'. Based on the answer key, certain questions get '1 point', certain questions get '0 points' and the mean hopelessness level is calculated with the arithmetic sum. Average score ranges from 0 to 20 points. Higher scores indicate higher level of hopelessness (**18**).

Multidimensional Scale of Perceived Social Support (MSPSS): The scale was developed by Zimet et al. (20). Turkish validity was made by Eker et al. (21). The scale is a data collection tool used to determine the level of SS. It is a seven-point Likert-type scale and comprises 12 items. The scale has three sub-dimensions: SS from family, friends and significant others (fiancée, partner, and lover). SS from the family is investigated in items '3-4-8-11', SS from friends is investigated in items '6-7-9-12', and SS from significant others is investigated in items '1-2-5-10'. The score range of each subscale is between 4-28 points. The total scale score is in the range of 12-84 points. Higher scores indicate higher level of perceived SS. The Cronbach's alpha coefficient (α) of the scale was determined as 0.86. Cronbach's alpha coefficients for sub-dimensions were determined as $\alpha = 0.83$ for family, $\alpha = 0.84$ for friends, and $\alpha = 0.88$ for significant others (**21**). In this study, Cronbach's alpha coefficient was reported to be $\alpha = 0.91$.

Data analysis was performed in digital environment using IBM SPSS Version 21.0 package program. Number, percentage, mean and standard deviation were used in the analysis of descriptive data. Normality was evaluated using the Shapiro–Wilk normality test. Mann–Whitney U test, Independent samples t test and Kruskal–Wallis test were used for comparison between groups. Spearman's correlation coefficient was used to examine the relationship between scale scores. Values with p less than 0.05 were considered significant.

The study was conducted according to the guidelines of the Declaration of Helsinki. Written permission was obtained from the Ege University Clinical Research Ethics Committee to conduct the study. Before applying the questionnaire, verbal and written consents were obtained from the parents participating in the study, explaining the purpose of this study.

RESULTS

Table 1 lists the distribution of sociodemographic characteristics of parents and children participating in this study. The average BHS score of the parents was reported to be 6.15 ± 4.23. Mean MSPSS subscale scores were 25.06 ± 5.33 for family, 22.52 ± 6.50 for friends, and 21.97 ± 7.25 for significant others. Mean MSPSS score of the parents was 69.55 ± 15.47.

BHS scores as per the age and sex of the parents ($p > 0.05$), a significant difference was reported between the BHS scores according to the education level of parents (p: 0.023). While the mean BHS score of the parents who were primary school graduates was high (7.13 ± 3.71), the mean BHS score of parents who were of university graduates was low (4.54 ± 3.37). No significant difference was reported between mean

http://dx.doi.org/10.36472/msd.v8i11.625

BHS scores of the parents as per the sociodemographic characteristics of children (p > 0.05).

Table 3 lists the comparison of sociodemographic characteristics of the parents and their children with the mean MSPSS scores. According to the results, no significant difference was reported between MSPSS scores of parents according to the sociodemographic characteristics (p> 0.05). A statistically significant relationship was reported between mean SS score of the parents obtained from the family and the ages of the children with CHD (p: 0.008). A significant difference was reported between the mean SS scores obtained from significant others according to the diagnoses of children with CHD (p: 0.044). No significant difference was reported between the mean MSPSS scores of the parents as per the sex of the children (p> 0.05).

Table 4 lists the relationship between the MSPSS scores and BHS scores of the mothers participating in this study. A moderate negative correlation was reported between the hopelessness level of the mothers and the perceived SS obtained from the family (r: −0.492, p: 0.00). Moreover, a weak negative correlation was reported between the hopelessness level and perceived SS from significant others (r: −0.349, p: 0.013) and overall perceived SS (r: −0.293, p: 0.039).

Table 5 lists the relationship between the MSPSS scores and BHS scores of the mothers participating in this study. A weak significant correlation was reported between the hopelessness level of the fathers and perceived SS from the family (r: 0.380, p: 0.06).

Table 1: Descriptive Characteristics (n = 100)

Sociodemographic Characteristics		Number (n)	Percent (%)
Sociodemographic Characteristics of Parents			
Gender	Female	50	50.0
	Male	50	50.0
Age	25 years and under	16	16.0
	26 years and older	84	84.0
Education Status	Primary school	15	15.0
	Middle School	26	26.0
	High school	35	35.0
	University	24	24.0
Sociodemographic Characteristics of Children			
Gender	Female	53	53.0
	Male	47	47.0
Age	0-1 Years	63	63.0
	2-3 years	31	31.0
	4-6 Years	6	6.0
Diagnosis	Acyanotic Heart Disease	49	49.0
	Cyanotic Heart Disease	51	51.0

Table 2: Comparison of Mean BHS Scores According to Sociodemographic Characteristics of Parents and Children (n = 100)

Variable		N	X ± SD	Test value	p value
Sociodemographic Characteristics of Parents					
Gender	Female	50	6.44 ± 4.51	U: 1183.500	0.644
	Male	50	5.86 ± 3.95		
Age	25 years and under	16	8.00 ± 4.64	t: 1.934	0.056
	26 years and older	84	5.79 ± 4.08		
Education Status	Primary school	15	7.13 ± 3.71	**KW: 9.549**	**0.023**
	Middle School	26	7.07 ± 4.46		
	High school	35	6.14 ± 4.60		
	University	24	4.54 ± 3.37		
Sociodemographic Characteristics of Children					
Gender	Female	53	6.07 ± 4.46	U: 1170.000	0.599
	Male	47	6.23 ± 3.99		
Age	0-1 years	63	5.68 ± 4.03	KW: 4.649	0.098
	2-3 years	31	6.67 ± 4.62		
	4-6 years	6	8.33 ± 3.77		
Diagnosis	Acyanotic	49	5.18 ± 3.31	U: 1029.500	0.126
	Cyanotic	51	7.07 ± 4.80		

BHS: Beck Hopelessness Scale, n: Number, X ± SD: Mean ± Standard Deviation, KW: Kruskal Wallis test, U: Mann Whitney U test, t: t test, p <0.05*

http://dx.doi.org/10.36472/msd.v8i11.625

Table 3. Comparison of Mean MSPSS Scores According to Sociodemographic Characteristics of Parents and Children (n = 100)

Variable		n	SS from Family X ± SD	SS from Friend X ± SD	SS From Significant Other X ± SD	Overall SS Score X ± SD
Sociodemographic Characteristics of Parents						
Gender	Female	50	25.24±5.65	22.84±6.64	22.88±7.10	70.96±15.82
	Male	50	24.88±5.04	22.20±6.41	21.06±7.35	68.14±15.15
			U:1104.00	U:1136.50	U:1013.00	U:1066.50
			p:0.262	p:0.420	p:0.091	p:0.200
Age	25 years and under	16	23.18±6.71	21.56±7.36	21.75±7.78	66.50±18.67
	26 years and older	84	25.41±4.99	22.70 ± 6.36	22.01±7.19	70.13±14.85
			t:-1.543	t:-0.641	t:-0.132	t:-0.859
			p:0.126	p:0.523	p:0.895	p:0.393
Education Status	Primary school	15	24.33±5.40	21.00±7.65	21.26±7.67	66.60±20.14
	Middle School	26	25.46±4.51	21.84±5.29	22.38±6.26	69.69±12.29
	High school	35	24.08±7.01	22.80±7.01	23.51±6.72	70.40±17.01
	University	24	26.50±2.35	23.79±6.27	19.70±8.45	70.00±13.61
			KW:1.35	KW:3.37	KW:3.33	KW:0.95
			p:0.716	p:0.337	p:0.343	p:0.813
Sociodemographic Characteristics of Children						
Gender	Female	53	24.47±6.17	21.84±7.10	21.90±7.50	68.22±17.28
	Male	47	25.72±4.15	23.27±5.73	22.04±7.04	71.04±13.17
			U:1105.00	U:1157.00	U:1217.00	U:1185.00
			p:0.281	p:0.528	p:0.839	p:0.672
Age	0-1 Age	63	25.74±4.77	23.01±6.27	22.57±7.07	71.61±14.25
	2-3 years	31	24.45±5.93	22.03 ±6.09	21.67±7.11	68.16±14.88
	4-6 Age	6	21.00±6.41	16.83±8.86	17.16±9.23	55.00±23.97
			KW:9.572	KW:5.60	KW:3.36	KW:4.98
			p:0.008 *	p:0.061	p:0.186	p:0.083
Diagnosis	Acyanotic	49	25.12±5.73	22.97±6.35	23.36±6.34	71.46±15.22
	Cyanotic	51	25.00±4.96	22.07±6.68	20.62±7.85	67.70±15.64
			U:1150.00	U:1118.5	**U:967.50**	U:1031.00
			p:0.444	p:0.351	**p:0.044 ***	p:0.127

MSPSS: Multidimensional Perceived Social Support Scale, SS: Social Support, n: Number, X ± SD: Mean ± Standard Deviation, KW: Kruskal Wallis test, U: Mann Whitney U test, t: t test, p < 0.05*

Table 4: The Relationship Between Mothers' MSPSS and BHS Scores (n = 50)

	r and p	SS from Family	SS from Friend	SS From Significant Other	Overall SS Score	Hopelessness
SS from Family	r	1.000				
	p					
SS from Friend	r	0.499	1.000			
	p	0.000				
SS From Significant Other	r	0.451	0.662	1.000		
	p	0.001	0.000			
Overall SS Score	r	0.622	0.872	0.887	1.000	
	p	0.000	0.000	0.000		
Hopelessness	r	**-0.492***	-0.130	**-0.349 ***	**-0.293***	1.000
	p	**0.000**	0.369	**0.013**	**0.039**	

MSPSS: Multidimensional Scale of Perceived Social Support, BHS: Beck Hopelessness Scale, SS: Social Support, r: Spearman Correlation Coefficient, p <0.05*

Table 5: The Relationship Between Fathers' MSPSS and BHS Scores (n = 50)

	r and p	SS from Family	SS from Friend	SS From Significant Other	Overall SS Score	Hopelessness
SS from Family	r	1.000				
	p					
SS from Friend	r	0.591	1.000			
	p	0.000				
SS From Significant Other	r	0.445	0.611	1.000		
	p	0.001	0.000			
Overall SS Score	r	0.694	0.865	0.880	1.000	
	p	0.000	0.000	0.000		
Hopelessness	r	**0.380***	-0.241	-0.073	-0.156	1.000
	p	**0.006**	0.092	0.613	0.278	

MSPSS: Multidimensional Scale of Perceived Social Support, BHS: Beck Hopelessness Scale, SS: Social Support, r: Spearman Correlation Coefficient, p <0.05*

DISCUSSION

This study was performed to examine the relationship between hopelessness levels and perceived SS levels of parents with children with congenital heart disease who underwent surgery.

In this study, the mean BHS score was reported to be 6.15 ± 4.23. Lowoko & Soares (15) examined hopelessness in parents with and without children with CHD and reported a mean BHS score as 4.8 ± 0.1. Similar results were reported in other studies conducted on parents (22, 23). Our results agree with the literature, and parents' perception of hopelessness was reported to be low.

When the differences between mean hopelessness levels according to parental education status were examined, the mean hopelessness level of primary school graduates (7.13 ± 3.71) was higher compared to individuals; however, the mean hopelessness level of university graduates was lower compared to other individuals (4.54 ± 3.37). A significant difference was reported between the mean hopelessness levels according to parental education level ($p < 0.05$). Akandere et al. (25), Durat et al. (26) and Yildirim & Yildirim (27) reported that parents who graduated from primary school had higher levels of hopelessness.

Çatalbaş et al. (28) reported that the hopelessness level of parents who received education was lower. The reason for the low level of hopelessness in parents with a high level of education may be that these parents have more information about their children's disease, treatment and care opportunities, and develop appropriate coping mechanisms and use problem-solving resources well in this process. For individuals with a low level of education, factors such as social status, roles in the society, not getting enough financial or moral support from their relatives, insufficient coping mechanisms, and not being able to benefit from existing resources can cause hopelessness.

In our study, perceived SS scores were reported to be high. MSPSS subscale mean scores were as follows: SS from the family was 25.06 ± 5.3, SS from friends was 22.52 ± 6.50, and SS from significant others was 21.97 ± 7.25. The overall SS score was 69.55 ± 15.47. Deveci & Ahmetoglu (24)'s results are similar to the results of this study.

When the differences between the MSPSS mean scores of the parents were examined as per the ages of children with CHD, the total scale and general SS scores of individuals with children in the 0–1 age group (71.61 ± 14.25) were reported to be higher than those of parents with children in other age groups. While there was no significant difference between the perceived SS levels received from friends and significant others as per the ages of children with CHD ($p > 0.05$), a significant difference was reported between the perceived SS levels received from the family ($p < 0.05$). Hoekstra-Weber et al. (29) examined perceived SS in parents of cancer patients and concluded that SS decreased over time. Most children with CHD are diagnosed and start treatment within the first year (4). Based on this proposition, the reason for the high levels of SS received from the family in children aged 0–1 years in this study may be attributed to the intensive diagnosis and treatment procedures in the first year.

Parents with a child with acyanotic CHD had higher scores on all subscales and the total scale (71.46 ± 15.22) compared to parents with a child with cyanotic CHD. In both groups, the perceived SS received from the family was reported to be high. No significant difference was reported between the perceived SS of parents received from the family and friends as per the diagnoses of children with CHD ($p > 0.05$); however, a significant difference was reported between the perceived SS received from significant others ($p < 0.05$). In the literature, there are differences in SS levels as per the severity of the disease. Almesned et al. (30) investigated SS in the parents of children with complex and mild congenital heart disease and reported that SS from families was higher in complex heart diseases. In this study, there was a difference between SS levels received from significant others, and families with children with cyanotic CHD had lower levels of SS from significant others (spouse, flirt, physician, and individual with the same experience). Azhar et al. (31) stated that parents with children with CHD require more information than given and that the emotional, moral and educational support physicians provide to parents can affect the quality of life of parents. In their meta-analysis, Lumsten et al. (32) stated that the support that parents with children with CHD give to each other and the support they receive from individuals with the same experience are important factors for coping mechanisms. Parents with a child with

cyanotic CHD may have high levels of anxiety and stress (33). Therefore, they may require more SS from significant others.

There was a significant negative correlation between mothers' hopelessness and SS from family and significant others and overall SS levels ($p < 0.05$). It can be stated that the level of hopelessness decreases as the level of SS from the family and significant others, as well as overall SS, increases. However, no significant relationship was reported between the level of hopelessness of fathers and the level of SS from friends and significant others and the overall SS. A positive and significant relationship was determined between the SS received from the family and the level of hopelessness ($p < 0.05$). As the level of SS received from the family increases, the level of hopelessness increases.

Similar to the results of mothers, there are studies in the literature showing a negative correlation between the level of hopelessness and perceived SS (8,11,12,13,34). Mothers require more SS than fathers to cope with hopelessness (15, 35). In this study, SS received from the family affects the hopelessness level of mothers by 49%. In a qualitative study conducted with parents with CHD, parents stated that their families assumed certain responsibilities during the course of the disease and provided physical support and emotional support. They stated that they received support from other individuals who had the same experience in increasing their hope during the course of the disease (36). In this context, the relationship between mothers' hopelessness and SS levels is consistent with the literature. However, the positive correlation between the hopelessness level of the fathers and SS received from the family is surprising. Generally, studies in the literature report a negative correlation between hopelessness and SS levels. Hoekstra-Weber et al. (29) examined SS and psychological adaptation in parents of pediatric cancer patients, and the fathers participating in the study stated that they received support during the course of the disease, but they cared more about being satisfied with the support rather than the level of SS received. In this context, our results are similar to the results of Hoekstra-Weber et al. (29).

The limitations of the study are that only volunteer patients participated in the study and the data were collected from single hospital.

CONCLUSION

There is a relationship between hopelessness and perceived SS levels in parents of children with CHD. SS received from the family plays a big role in the parents' level of hopelessness. Creating sources of physical, emotional, spiritual, and informational support for parents during treatment of CHD can increase their level of SS and reduce the level of hopelessness. In this context, it is recommended to provide family-centered care for parents, to increase communication with family members, to meet their educational requirements with the help of healthcare professionals, to increase communication with individuals who have had the same experience, and to provide psychosocial support.

Author Contributions: TNO, RC: Research of the literature, **TNO;** Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Global Burden of Disease Study (GBD) 2017 Congenital Heart Disease Collaborators. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. Child & Adolescent Health 2020;4(3):185–200.

2. Gilboa SM, Salemi JL, Nembhard WN, Fixer DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. Circulation 2020;122(22):2254-63.

3. Oster ME, Lee KA, Honein MA, Riehle-Colorusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics 2013;131(5): 1502-8.

4. Centers for Disease Control and Prevention (CDC) (2019, November 12). Congenital heart defects (CHDs). Access address: http://www.cdc.gov/ncbddd/heartdefects/data.html. Date of access: 09.12.2020.

5. Kolaitis GA, Meentken MG, & Utens E. Mental health problems in parents of children with congenital heart disease. Frontiers in Pediatrics 2017; 5:102.

6. Harvey KA, Kovalesky A, Woods RK, Loan RA. Experiences of mothers of infants with congenital heart disease before, during, and after complex cardiac surgery. Heart & Lung 2013; 42:399-406.

7. Biber S, Andonian C, Beckmann J, Ewert P, Freilinger S, Nagdyman N et al. Current research status on the psychological situation of parents of children with congenital heart disease. Cardiovascular Diagnosis and Therapy 2019;9(2):369–76.

8. Yagmur Y & Oltuluoglu H. Social support and hopelessness in women undergoing ınfertility treatment in eastern Turkey. Public Health Nursing 2012;29(2): 99-104.

9. Ozer Gok F, Tascı Beydag KD, Cengiz S, Kiper S. Hopelessness levels of patients undergoing hemodialysis. Fırat Health Services Journal 2009;4(10):123-35.

10. Ayaz S, Yaman ES, Korukluoglu S. Level of perceived social support of patients with gynaecological cancer and affecting factors. Türkiye Klinikleri Journal Medicine Sciences 2008; 28:880-5.

11. Madani H, Pourmemari M, Moghimi M, Rashvand F. Hopelessness, perceived social support and their relationship in Iranian patients with cancer. Asia-Pasific Journal of Oncology Nursing 2018;5(3): 314-19.

12. Pehlivan S, Ovayol O, Ovayol N, Sevinc A, Camci C. Relationship between hopelessness, loneliness, and perceived social support from family in Turkish patients with cancer. Support Care Cancer 2012;20(4):733-9.

13. Yildirim H, Isik K, Firat TY, Aylaz R. Determining the correlation between social support and hopelessness of Syrian refugees living in Turkey. Journal of Psychosocial Nursing and Mental Health Service 2020;58(7): 27-33.

14. Deng L, Wang H, Chen J, Li L. Social support and negative emotion in parents of children with congenital heart disease before operation. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2013;38(9): 915-9.

15. Lawoko S, Soares JJF. Distress and hopelessness among parents of children with congenital heart disease, parents of children with other disease, and parents of healthy children. Journal of Psychosomatic Research 2002; 52:193-208.

16. Silva GVD, Moraes DEB, Konstantyner T, Leite HP. Social support and quality of life of families with children with congenital heart disease. Ciência & Saùde Coletiva 2020;25 (8):3153-62.

17. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: The hopelessness scale. Journal of Consulting and Clinical Psycholgy 1974;42: 861-65.

18. Seber G, Dilbaz N, Kaptanoğlu C, Tekin D. The hopelessness scale: validity and reliability. Journal of Crisis 1991;1(3): 139-42.

19. Durak A, Palabıyıkoglu R. Beck hopelessness scale validity study. Turkish Journal of Psychology 1994; 9(31):1-11.

20. Zimet G, Dahlem N, Zimet S, Farley G. The multidimensional scale of perceived social support. Journal of Personality Assessment 1988;52(1):30-41.

21. Eker D, Arkar H, Yaldız H. Factorial structure, validity, and reliability of revised form of the multidimensional scale of perceived social support. Turkish Journal of Psychiatry 2001;12(1):17-25.

22. Kostak MA, Avci G. Hopelessness and depression levels of parents of children with cancer. Asian Pacific Journal of Cancer Prevention 2013;14(11),6833-8.

23. López R, Frangini P, Ramírez M, Valenzuela PM. Well-being and agency in parents of children with congenital heart disease: a survey in chile. World Journal for Pediatric and Congenital Heart Surgery 2016;7(2):139-45. doi:10.1177/2150135115623284.

24. Deveci M, Ahmetoglu E. Examination of the level Perceived social support by the families with mentally retarded children. Balkan and Near Eastern Journal of Social Sciences 2018;4(2):123-31.

25. Akandere M, Acar M, Baştug G. Investigating the hopelessness and life satisfaction levels of the parents with mentally disabled child. Selçuk University Social Sciences Institute Journal 2009; 12:24-32.

26. Durat G, Atmaca GD, Unsal A, Kama N. Hopelessness and depression in the families of children with special needs. Osmangazi Medical Journal 2017; 39(3): 49-57.

27. Yildirim A, Yildirim MS. Hopelessness of mothers who have children with Down syndrome. Genetic Counseling 2010;21(4): 375.

28. Catalbas M, Greengrocer G, Ocakçı AF. Family-oriented nursery approach to despair levels of the parents of children with cardiac disease and down syndrome . Marmara University Institute of Health Sciences Journal 2015;5(3): 154-61.

29. Hoekstra-Weebers JE, Jaspers JP, Kamps WA, Clip EC. Psychological adaptation and social support of parents of pediatric cancer patients: A prospective longitudinal study. Journal of Pediatric Psychology 2001; 26:225-35.

30. Almesned S, Al-Akhfash A, Mesned AA. Social impact on families of children with complex congenital heart disease. Annals of Saudi Medicine 2013;33(2):140–43.

31. Azhar AS, Alshammasi ZH, Higgi RE. The impact of congenital heart diseases on the quality of life of patients and their families in Saudi Arabia. Biological, psychological, and social dimensions. Saudi Medical Journal 2016;37(4),392-402.

32. Lumsden MR, Smith DM, Wittkowski A. Coping in parents of children with congenital heart disease: a systematic review and meta-synthesis. Journal of Child and Family Studies 2019; 28:1736-53.

33. Uzger A, Baspınar O, Bulbul F, Yavuz S, Kilinc M. Evaluation of depression and anxiety in parents of children undergoing cardiac catheterization. Archieves of the Turkish Society of the Cardiology 2015;43(6):536–41.

34. Eslami B, Kovacs AH, Moons P, Abbasi K, Jackson JL. Hopelessness among adults with congenital heart disease: Cause for despair or hope?. International Journal of Cardiology 2017;230:64-9.

35. Bayat M, Erdem E, Gul Kuzucu E. Depression, anxiety, hopelessness, and social support levels of the parents of children with cancer. Journal of Pediatric Oncology Nursing 2008;25(5):247-53.

36. Golfenshtein N, Deatrick JA, Lisanti AJ, Medoff-Cooper B. Coping with the stress in the cardiac intensive care unit: can mindfulness be the answer? Journal of Pediatric Nursing 2017; 37:117-26.

MSD

Medical Science and Discovery
ISSN: 2148-6832

Acute and chronic toxicity of ethyl chloride insufflation in two patients

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ABSTRACT

Objective: Inhalant abuse has been a source of increasing concern because of its easy accessibility and affordability. Anecdotal reports have previously described ethyl chloride as a potential cause of altered mental state and neurologic symptoms. Its use has been thought to be found most often in adolescents and among men who have sex with men. Common acute symptoms include confusion, dizziness, headache, nausea, and fatigue. We describe two cases of adult patients who presented to one general hospital emergency department with ethyl chloride toxicity. The first presented with acute delirium; the second with a picture of chronic neurological symptomatology. It is important that clinicians become familiar with ethyl chloride intoxication because of its prevalence and potential to present with varying acute and chronic symptomatology.

Key words: Inhalation exposure, ethyl chloride, drug toxicity

INTRODUCTION

Inhalant abuse has been an increasing source of concern because of its easy accessibility and affordability (1). Ethyl chloride is a clear, colorless volatile vapour once used as a general anesthetic but which is now commonly found and readily available in spray form as a topical anesthetic, refrigerant, and solvent. Its use as a recreational inhalant is believed to be increasing although its precise prevalence is unknown. Most reports focus on the abuse of ethyl chloride as a euphoriant among adolescents and young adults (2, 3). Documented symptoms of acute ethyl chloride inhalation include confusion, dizziness, headache, nausea, and fatigue. Long-term insufflation of ethyl chloride can cause significant neurotoxicity including visual hallucinations, nystagmus, dysarthria, lack of voluntary muscle control, intention tremors, and ataxia. We here describe two middle-aged adults who presented at one institution and who illustrate the effects of both acute and chronic abuse.

1. Case of acute ethyl chloride inhalation

A 49-year-old man with a history of bipolar disorder was brought to the emergency department with drowsiness, agitation, and confusion. According to the patient's family, he was in his usual state of health until one week prior this presentation at which time he developed slurred speech and emanated a strange odor. He exhibited increasing confusion over the next several days including evident visual hallucinations and the delusion that he had been evicted from his home. He was noted to be packing his belongings to prepare for this imagined eventuality.

On the day of admission, patient's family found a total of 12 empty cans of ethyl chloride in the garbage bin next to the patient's bed. The patient was noted to have a blank stare with drooping eyelids, unintelligible speech, and rapid breathing. He was transferred to the emergency department. On physical examination, the patient was awake but agitated. Vital signs were notable for tachycardia of 110 bpm and tachypnea with a respiratory rate of 30. He was afebrile and normotensive. Routine urine toxicology screening was negative. Serum concentration of ethyl alcohol was less than 10 mg/dL. Chemistry and arterial blood gas determinations revealed a mixed acid-base disturbance with severe respiratory alkalosis and metabolic acidosis with a pH of 7.38, pO_2 of 71, and pCO_2 of 16 but with a normal anion gap. Electrocardiography displayed a normal sinus rhythm. Neuroimaging was not performed.

Case Report Article

Received 29-09-2021

Accepted 08-10-2021

Available Online: 12-10-2021

Published 30-11-2021

http://dx.doi.org/10.36472/msd.v8i11.606

Shortly after admission, patient began to have increased secretions, compromising his airway. He required endotracheal intubation and was transferred to the intensive care unit (ICU). During the ensuing 48 hours, his alertness improved, and his agitation abated. He was oriented and spoke in complete sentences.

His clinical course in the ICU was complicated only by mild azotemia that resolved over the next several days. He was placed back on his baseline psychiatric medications of bupropion and quetiapine. He was discharged in a stable and improved state. Two weeks after discharge, the patient was seen at an outpatient clinic. He reported abstinence from ethyl chloride inhalation and was observed to have resolution of his psychiatric and respiratory symptoms.

2. Case of chronic ethyl chloride inhalation

A 62-year-old man with a history of major depression and anxiety presented to the emergency department with new-onset diplopia of one-month duration. He also reported upper extremity tremors, tongue spasticity, and gait instability. One month prior to his presentation, the patient was seen at an outpatient clinic and was noted to have ataxia and memory impairment, which continued to persist. The patient's past medical history was significant for alcohol and substance dependency, with a self-reported abstinence of more than a decade.

On physical examination, the patient was awake and alert. Vital signs were within normal limits. The patient's thinking was tangential, and he was observed at times to respond to internal stimuli. On cognitive assessment, the patient was oriented to person but not to place or time. Memory and clock drawing were markedly impaired.

The patient had full extraocular movements without nystagmus but right-sided facial droop with nasolabial fold flattening, slurred speech, intention tremor, wide-based ataxia, diffuse hyperreflexia and a positive Romberg sign. Laboratory results were unremarkable. Urine drug screen was positive for cannabinoids only. Serum ethanol level was undetectable. Electrocardiogram incidentally revealed the presence of atrial flutter with rapid ventricular response. A subsequent nuclear stress test was negative. Both non-contrast CT of the head and MRI of the brain were negative.

After finding no clear aetiology for his symptoms, a more detailed history was pursued by the medical resident. The patient revealed the chronic use of ethyl chloride several times per week for one year. The patient received supportive therapy for his symptoms.

He was started on an antipsychotic, olanzapine 5 mg by mouth daily, for his disorganization. His atrial flutter returned to normal sinus rhythm after cardioversion and amiodarone therapy. Over the following several days, the patient's upper extremity tremors, tongue spasticity, and gait instability resolved.

The patient was advised to discontinue ethyl chloride use. Olanzapine was discontinued. The patient has been followed by his primary care physician and psychiatrist for several months without any recurrence of neurological symptoms.

DISCUSSION

Ethyl chloride (C_2H_5Cl), or chloroethane, is a colorless volatile vapor with a characteristic ether-like odor.4 It has historically been used as a general anesthetic in major surgeries. Due to the risk of accidental death, ethyl chloride is no longer medically used to induce a state of sedation. Currently, it is used as a topical anesthetic in the form of a spray. It is also used as a refrigerant, solvent, and alkylating agent.

Ethyl chloride can be purchased both online and in stores as a legitimate household product or as drug paraphernalia (e.g., Maximum Impact, Black Max Heavy Duty, Black Jac, Ethyl Gaz, Ethyl Four Star, Jungle Juice Plus, Rush, and Macho). Hence, it has increasingly become an agent of choice for recreational "sniffing" (**5, 6**). A Singapore American School newspaper released a video report that demonstrated the ease of obtaining "EC" by high school students due to its easy accessibility and affordability. A student reported that when he got high from "EC", he felt as if everything slowed down, that he became more aware of his heartbeat, and that he simply could not keep himself from laughing (**7**) Inhalants are the second most prevalent illicit substance among 8th graders in the United States according to the Monitoring the Future study in 2018 by the University of Michigan (**2, 3**). Although the prevalence of ethyl chloride use among adults is not well documented, there are reports of its use and abuse to enhance sexual pleasure among men who have sex with men (**8**).

Inhaled ethyl chloride is readily absorbed through the lungs. Its lipophilic nature allows it to cross the blood brain barrier, accumulating in the brain at a concentration two times that of blood (**9**) Studies on rats have shown that ethyl chloride is metabolized by cytochrome P450 to acetaldehyde and is then metabolized either to acetic acid or, by the conjugation of ethyl chloride with glutathione, to S-ethyl-glutathione, which is excreted in the urine.

Unmetabolized ethyl chloride is exhaled through the lungs accounting for its characteristic odor. Animal studies have also shown that ethyl chloride can enhance the effects of alcohol (**5**). This finding is consistent with the observation that at acute high levels of ethyl chloride gas exposure, temporary feelings of drunkenness, lack of muscle coordination, and unconsciousness are produced. Other potential symptoms of acute overexposure include cardiac arrhythmias and cardiac arrest (**4, 5**).

Long-term insufflation of ethyl chloride can also cause significant neurotoxicity. Symptoms that have been reported related to chronic abuse include visual hallucinations, nystagmus, dysarthria, lack of voluntary muscle control, intention tremors, and ataxia (**6,10-13**). There are 3 reported deaths due to ethyl chloride insufflation (**1, 14, 15**).

Our first patient's non-anion gap metabolic acidosis was likely due to ethyl chloride toxicity, similar to the non-anion gap metabolic acidosis reported with toluene inhalation. In toluene metabolism and elimination, the metabolite hippurate is filtered and secreted into the renal tubule and then rapidly excreted in the urine, preventing a plasma build-up of organic acids, which would lead to an increased anion gap (**17**).

This explanation is further supported as the acid-base disorder rapidly resolved after ethyl chloride abstinence.

Studies in dogs have shown cardiac irregularities from acute exposure to anaesthetic concentrations of ethyl chloride (**15, 16).** Given that the second patient had no significant cardiac history or other identifiable aetiology, his atrial flutter was most likely associated with ethyl chloride inhalation. While cannabis may cause mental status changes, intoxication is often short-lived and does not produce the neurological signs and symptoms seen in this patient.

Diagnosis is based on high clinical suspicion and unremarkable imaging and laboratory workup (except, perhaps, the above noted non-anion gap acidosis). There are no commonly used medical tests available to determine exposure to ethyl chloride. One recent forensic study presented a 40-year-old man found unresponsive after ethyl chloride inhalation, confirmed by performing a dynamic headspace gas chromatography coupled to mass spectrometry. Ethyl chloride levels were detected in peripheral and central blood and lung and brain tissues (**1**). However, while gas chromatography exists and can be used for confirmation by measuring ethyl chloride levels in blood, milk, and urine, it is not readily available in the clinical setting.

The mainstay of managing ethyl chloride intoxication has been largely based on supportive care measures. In reported cases of chronic inhalation of ethyl chloride that resulted in neurotoxicity, symptoms resolved days to weeks after cessation of ethyl chloride inhalant abuse, similar to the course our second patient. It has been noted that unconscious patients breathing spontaneously may recover by the time they arrive in the emergency department if the toxic state is due to isolated ethyl chloride toxicity. Persistent unconsciousness should prompt assessment of the presence of other substances of abuse. There appears to be no withdrawal state associated with the discontinuation of ethyl chloride use.

CONCLUSION

We believe that both our patients' neurotoxic symptoms were associated with ethyl chloride insufflation. Both had unremarkable urine drug screens. Both patients admitted to using ethyl chloride, and cessation resulted in the resolution of symptoms, as noted in other published case reports.

Physicians should become familiar with the toxic symptoms associated with ethyl chloride and other inhalants of abuse. Acute presentations can manifest as delirium, acid-base abnormalities, hyperventilation, or cardiac arrhythmias. More chronic use appears to display more focal neurologic signs such as tremors, ataxia, and hyperreflexia. Atrial or ventricular arrhythmias, including reports of ventricular fibrillation, are possible with either acute or chronic use. Although inhalant abuse has been shown to be most prevalent among adolescents, clinicians should recognize a growing use among older patients as well, particularly among men who have sex with men. Supportive measures are the mainstay of management. Efforts directed towards rehabilitation, psychiatric evaluation, and counselling for substance abuse are of key importance. Indeed, since many cases demonstrate a near-complete recovery following discontinuation of ethyl chloride insufflation, stressing cessation can prevent the very serious consequences of ethyl chloride abuse.

Author Contributions: JV, JML: Research of the literature, Patient examinations, Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Pascali J, Fais P, Viel G, Cecchetto G, Montisci M. Is old stuff back? A fatal case of ethyl chloride sniffing. Egyptian Journal Of Forensic Sciences. 2019; 9(1):29. https://doi.org/10.1186/s41935-019-0136-4.

2. Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the future national survey results on drug use, 1975-2018: volume I, secondary school students. Ann Arbor: University of Michigan, Institute for Social Research; 2019. 586 p.

3. Schulenberg JE, Johnston LD, O'Malley PM, Bachman JG, Miech RA, Patrick ME. Monitoring the future national survey results on drug use, 1975–2018: volume II, college students and adults ages 19–60. Ann Arbor: University of Michigan, Institute for Social Research; 2019. 505p.

4. Merck, Sharpe, and Dohme. The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th ed. Whitehouse Station, NJ: Merck and Co., Inc.; 2001. 2165p.

5. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for chloroethane (Update). Atlanta, GA: Public Health Service, U.S. Department of Health and Human Service; 1998. 20p.

6. Finch C, Lobo B. Acute inhalant-induced neurotoxicity with delayed recovery. Ann Pharmacother. 2005;39:169-172.

7. The Eye. Ethyl Chloride, or EC, is new off-the-shelf high. 2014, May 19. https://youtu.be/l1Z9RKDOzOk.

8. Hall TM, Shoptaw S, Reback CJ. Sometimes poppers are not poppers. Huffing as an emergen health concern among MSM substance abusers. J of Gay Lesbian Ment Health. 2014; 19:118-121.

9. Konietzko H. Chlorinated ethanes: Sources, distribution, environmental impact and health effects. Hazard Assessment of Chemicals.1984; 3:401-448.

10. Soult T, Walker J. Ethyl chloride intoxication. Am J Emerg Med. 1993;11:313-315.

11. Nordin C, Rosenqvist M, Hollstedt C. Sniffing of ethyl chloride – an uncommon form of abuse with serious mental and neurological symptoms. Int J Addict. 1988;23:623-627.

12. Demarest C, Torgovnick J, Sethi N, Arsura E, Sethi P. Acute reversible neurotoxicity associated with inhalation of ethyl chloride: a case report. Clin Neurol Neurosurg. 2011;113:909-910.

13. Broussard L, Broussard A, Pittman T, Lirette D. Death due to inhalation of ethyl chloride. J Forensic Sci. 2000;45:223-225.

14. Yacoub I, Robinson C, Simmons G, Hall M. Death attributed to ethyl chloride. J Anal Toxicol. 1993;17:384-385.

15. Haid B, White JM, Morris LE. Observations of cardiac rhythm during ethyl chloride anesthesia in the dog. Curr Res Anesth Analg. 1954; 33(5):318-325.

16. Morris TE, Tasto WD. 1979. Ethyl chloride. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology. 3rd ed. Vol. 5. New York, NY: John Wiley and Sons. p714-722.

17. Carlisle EJ, Donnelly SM, Vasuvattakul S, Kamel KS, Tobe S, Halperin ML. Glue-sniffing and distal renal tubular acidosis: sticking to the facts. J Am Soc Nephrol 1991; 1(8):1019-1027.

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International Journal of
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