CLINICAL NEUROSCIENCE

75. ÉVFOLYAM 5–6. SZÁM • 2022. MÁJUS 30.

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OFFICIAL JOURNAL
of the
Hungarian Neurological Society,
Hungarian Neurosurgical Society,
Hungarian Society of Clinical Neurophysiology,
Hungarian Society of Child Neurology,
Hungarian Society of Neuroradiology,
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and Hungarian Neuroscience Society

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A Magyar Neurológiai Társaság,
a Magyar Idegsebészeti Társaság,
a Magyar Klinikai Neurofiziológiai Társaság,
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és a Magyar Idegtudományi Társaság
HIVATALOS LAPJA

L M

Ideggyógyászati Szemle/Clinical Neuroscience
havonta megjelenő szakfolyóirat
Impakt faktor: 0,427 (2020)

ISSN 0019-1442

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SAJTÓKÖZLEMÉNY

ÚJ TECHNOLÓGIÁK, ROBOTIZÁLT ESZKÖZÖK A REHABILITÁCIÓBAN

2022. ÁPRILIS 6.

Az Országos Mozgásszervi Intézet Rehabilitációs Telephelyének (OMINT-OORI) célkitűzése, hogy olyan új eljárások és technológiák hazai alkalmazásának bevezetését segítse, amelyek Magyarországon a közfinanszírozott ellátásban még nem elérhetők. Az elnyert több mint 1,264 milliárd forint vissza nem térítendő európai uniós támogatás segítségével az Intézet olyan humánkineziológiai laboratóriumot hozott létre, amely diagnosztikai (mozgáselemzés) és fejlett technológián alapuló terápiás eszközökkel dolgozik. Ezeket az eszközöket a komplex rehabilitációs program keretében, a hagyományos eljárásokkal összehangolva alkalmazza. Az új technológiával megismerteti az egyetemi hallgatókat és a már végzett szakembereket is.

Az OMINT-OORI nemcsak országosan, hanem nemzetközi viszonylatban is ismert rehabilitációs szakmai intézmény, mely elkötelezett a modern technológiák és kutatások iránt. Az „Országos Intézetek transznacionális és innovációs fejlesztései” nevű projekt a Széchenyi 2020 program keretében valósult meg.

A pályázaton elnyert több mint 1 milliárd 200 millió forintból elsősorban eszközbeszerzésre került sor. A fejlesztés eredményeként kiépítésre került egy új központi humánkineziológiai laboratórium, ami a kezelési terv alapján fogadja a betegeket, és közel 20 eszköz került a fekvőbeteg-ellátó osztályokra, ahol azokat a mindennapi terápiák szerves részeként használják a kollégák. A robotok által alkalmazott rendszer a gyakorlatok nagyszámú ismétlése miatt hatékonyabban javíthatja a mozgásokat, így nagy előnye van a mozgás automatizálásában. Többek között olyan robotasszisztált rehabilitációs rendszert vezetnek be először hazai közfinanszírozott intézményben, amely féloldali vagy teljes izomgyengeséggel, bénulással járó traumás gerincvelő-sérülést vagy agyvérzést szenvedett személyek járás-újratanulásának elősegítését szolgálja.

A megszerzett ismereteket az Intézet megismerteti az egyetemi hallgatókkal és a már végzett szakemberekkel is.

A fejlesztés eredményeként az európai uniós támogatás segítségével 2022 végére olyan új eljárások, módszerek jelennek meg a súlyos sérültek kezelésében, melyek ez idáig nem voltak jelen a magyarországi neurorehabilitációs ellátásban.

A fejlesztés célja, hogy megtörténjen az új eljárások hazai bevezetése, amelyek idővel a közfinanszírozott ellátásban is elérhetővé válhatnak.

A projektről bővebb információt
a www.rehabint.hu oldalon olvashatnak.

További információ kérhető
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A projekt kezdete: 2021. 02. 01.
A projekt tervezett befejezési dátuma: 2022. 12. 31.
A projekt azonosítószáma: EFOP-5.2.6-20-2020-00012

POSTURE CORRECTION AS PART OF HOLISTIC HEALTH PROMOTION IN HUNGARIAN SCHOOLS

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English https://doi.org/10.18071/isz.75.0151 www.elitmed.hu

The primary prevention program of the Hungarian Spine Society was launched in 1995 with two goals: 1. to achieve that all school-children take part regularly in effective posture correcting exercises as part of physical education; and 2. to achieve daily physical education for all school-children. With appropriate governmental legislation and parliamentary decision both goals were integrated into the National Public Health Program in 2001 and 2003 and later in the national educational laws and documents. From 2011 and 2012 holistic health promotion in schools with the goal to reach all children became also prescription for all schools in Hungary. Public health institutions and actors still have to do much: they have to give continuous professional help to the physical education teachers in their posture correcting work and to all teachers in their daily health promoting tasks.
The article presents the details of the special posture correcting exercises, their distribution and prospective controlled studies, their place in the national education, the present situation and the further tasks. The article is supplemented by a short report about daily physical education and holistic health promotion in schools: how the prescription was achieved, the essence and the follow up of it, and what are the tasks for the helping public health actors.

Keywords: *biomechanically correct posture, sagittal balance, posture correction, daily physical education, holistic health promotion in schools*

TARTÁSKORREKCIÓ A TELJES KÖRŰ ISKOLAI EGÉSZSÉGFEJLESZTÉS RÉSZEKÉNT
Somhegyi A, MD, PhD
Ideggyogy Sz 2022;75(5–6):151–161.

A Magyar Gerincgyógyászati Társaság prevenciós programja 1995-ben indult két célkitűzéssel: minden iskolás tanuló vegyen részt rendszeresen a hatékony tartásjavításban a testnevelési óra keretében; a mindennapos testnevelés váljon jogszabályi előírássá és ezáltal váljon minden tanuló hasznára. Kormányzati és országgyűlési jogi szabályozás útján mindkét cél része lett a 2001-ben indított Egészséges Nemzetért Népegészségügyi Programnak, majd később a köznevelési jogszabályoknak. 2011, illetve 2012 óta a teljes körű iskolai egészségfejlesztés is előírás minden iskola részére. A népegészségügyi szereplőknek most szakmai segítséget kell nyújtaniuk a testnevelők részére a tartáskorrekció helyes végzésében, illetve minden pedagógusnak az egészségfejlesztési tennivalókban. A közlemény a speciális tartáskorrekció részleteit, terjesztését, kontrollált vizsgálatát, a köznevelésben elfoglalt jelen helyzetét és a további tennivalókat ismerteti. A közlemény kiegészítő része a mindennapos testnevelésről, valamint a teljes körű iskolai egészségfejlesztésről ad rövid tájékoztatást: hogyan sikerült elérni a kötelező előírást, mi a lényege, hogyan történik a nyomon követése és mik a további népegészségügyi tennivalók.

Kulcsszavak: *biomechanikailag helyes testtartás, nyílirányú egyensúly, tartáskorrekció, mindennapos testnevelés, teljeskörű iskolai egészségfejlesztés*

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Érkezett: 2021. február 18. Elfogadva: 2021. március 23.

The importance of the biomechanically correct posture can not be overstated. Physical inactivity and the sedentary lifestyle that is unfortunately common among children and adolescents results in weakened and shortened postural muscles due to little or incorrect use. Thus, the proper balance among posture muscles is not achieved, and the gravitational load affects the small structural components of spine, which are not able to endure the strain. (Proper muscle balance ensures that the load

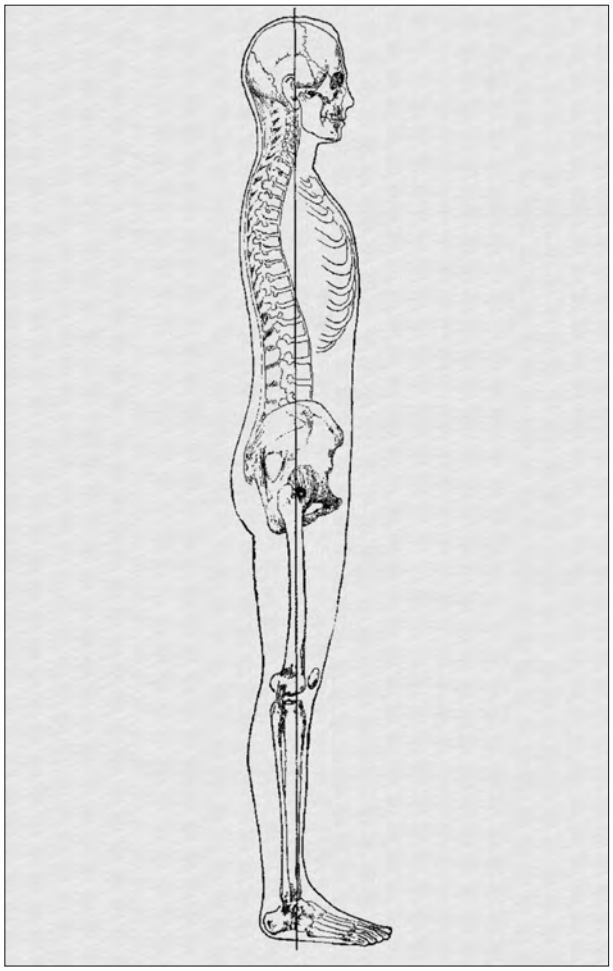

Figure 1. *The biomechanically correct posture is based on a correct middle position of the pelvis and the physiological sagittal curves above it. From the side view, the imaginary weight median of the body crosses the 2nd to 5th cervical and the 2nd to 5th lumbar vertebral bodies, which are relatively large bony components adapted for this, while the thoracic kyphosis assists flexibility*

falls upon components of spine which are capable of enduring the strain.) Muscle imbalance and overloading certain elements of spine can cause degenerative spinal disorders. Degenerative changes in the overloaded intervertebral discs cause pathological hypermobility in facet joints, and then these two processes accelerate each other. Later spinal stenosis can occur because of the above mentioned degenerative changes of the discus and the facet joints.

Dynamic balanced posture – i.e., alignment of body parts – is maintained by invisible, multidirectional functions of postural muscles[1, 2]. Biomechanically correct posture[1, 3, 4] occurs when there is physiological tension on joint capsules and ligaments with a minimum amount of muscular effort because of the balanced interaction of the postural muscles. Thus, the pressure on the articular surface of joints is evenly distributed. The biomechanically correct posture is based on a correct middle position of the pelvis and the physiological sagittal curves above it **(Figure 1)**. There are several types of incorrect posture where the lumbopelvic sagittal balance is impaired **(Figure 2)**.

Posture being an automatism, developing and maintaining the automatism of biomechanically correct posture gives the basis for primary prevention of discopathy. The aim of application of special exercises in physical education is to develop, automatize, and maintain biomechanically correct posture.

Some data of physical evaluations among preschool children and students

The physically inactive, sedentary lifestyle of today's children and adolescents has become remarkably prevalent: according to *Pellet,* 62% of preschoolers have bad posture, and this figure increases over the school years. According to *Fejérdy,* the rate of poor posture or other orthopedic disorders was 66% in 1991, 73% in 1992, and 78% in 1996 among high school students, and 88% among primary and secondary school students in 1999[5]. According to *Simóné Rőth* et al. in 2010, 70% of the 900 student evaluated had various physical spine deviations which required regular spine-exercises[6]. *Boja* et al. reported some results of the Genodisc Project (see later) also in 2010, according to which there were numerous students with poor posture (64.5% of evaluated students with bad posture in the premeasurement)[6]. 60% of pre-schoolers in Germany have sceletal muscle weakness according to *Weiss*[7], and *Kapo*[8] – based on his

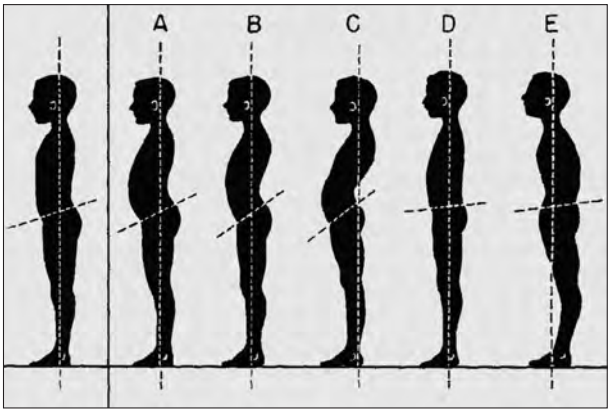

Figure 2. *Correct and several poor (A-E) postures*

objective measurements –, showed the correlation between the deformities of several parts of the body.

The Essence of the Hungarian Spine Society's Prevention Program

To compensate sedentary lifestyle and it's harm on the spine, daily regular physical activity, as well as automatizing and maintaining correct posture from childhood on, may prevent degenerative spinal disorders or delay their onset. Automatizing and maintaining correct posture may work best if special physical exercises are regularly applied since childhood. This is why daily physical education (DPE) and, within that, regularly performed special posture correction exercises for all schoolchildren are needed.

To improve the children's chance for a healthy life, the Hungarian Spine Society (HSS) launched its Prevention Program in 1995 with two goals: that schools offer DPE classes and teach special posture correction exercises to every student in DPE. The Prevention Program was based on the international and national medical literature and started in full agreement with all associate professions[9].

The essence of the HSS's Prevention Program is to show physical education teachers the special posture correction exercises that are to be taught to all schoolchildren (preferably also to kindergartners) as part of their daily physical education throughout the school years in order to develop and automatize the biomechanically correct posture, thereby contributing to the prevention of degenerative spinal disorders in adulthood. The special exercises were created by leading physiotherapists. The theoretical background and literature of this special posture correction exercises was reported in 2005[10]. The exercises were designed to develop and maintain the muscle balance (i.e. appropriate flexibility and strength of the muscles responsible for posture) and the correct mid-position of the pelvis. Thus, the exercise program targets all the postural muscles (stretch and strengthen), not only the well-known weak abdominal and back muscles. In order to develop and maintain the correct posture, exercises must be necessarily complex to impact several muscles and to improve global muscle balance. The special exercise program is based on 12 goal-exercises that may function as test-exercises as well **(Figure 3)**. These 12 semi-objective muscle tests evaluate whether the subject is able to perform the exercises in the correct way. If one is able to per-

Figure 3. *The special posture correcting exercise program of HSS is based on 12 goal - or test-exercises, as these show the strength and flexibility of postural muscles. There are 3-5 developing exercises belonging to all goal - or test - exercises. Physical education teachers have to apply the exercise-blocks one after another, continuously in the whole school year – so it does not take too long time but the regular and repetitive performance will develop the muscle balance. Performance must be precise*

form all these 12 test-exercises perfectly, he or she has postural

muscle balance: all postural muscles are appropriately flexible and strong.

The whole exercise program consists of 52 exercises, which are to develop all muscle groups responsible for posture. The exercises are placed in 11 blocks, in which after several developing exercises, the goal/test exercises are also located:

1. conscious sensation of the correct posture in standing position;
2. strengthening (and stretching) certain parts of neck and shoulder girdle (with the goal/test exercise No.2);
3. common strengthening of deep back muscles and hip extensors (with the goal/test exercise No.3);
4. strengthening certain parts of abdominal muscles (with the goal/test exercises No.4 and 5);
5. strengthening antigravity muscles of the lower limb (with the goal/test exercises No.1 and 6);
6. stretching deep back muscles (with the goal/test exercise No.7);
7. stretching abdominal muscles and hip flexors (with the goal/test exercise No. 8);
8. increasing the rotation of the lower thoracic and lumbar spine: stretching pectoral muscles, m. adductores, and m. tensor fasciae latae, strengthening and stretching the oblique abdominal muscle (with the goal/test exercise No.9);
9. stretching the hamstring muscles (with the goal/test exercise No.10);
10. increasing the mobility of hip joint and stretching the hip-flexores (with the goal/test exercises No.11 and 12);
11. practicing the awareness of the correct posture.

Teachers of physical education have to use the 1st block in every physical education (PE) class and then one of the following blocks, so after 11 PE classes the blocks will be repeated. With this repetitive and regular method the exercises will develop, automatize and maintain the muscle balance and this can be detected e.g. in improving muscle tests of muscle balance.

As a result of continued government support between 1995 and 2004, the physical education teachers could take part in trainings of the posture correction exercises throughout the whole country and were given the introductory exercise booklet and DVD 1, 2 and 3 – all free of charge[11, 12]. DVD1 is an educational film: after the 12 muscle test-exercises the whole exercises are presented, showing the correct and incorrect ways to perform and explaining the details. One is not supposed to do the exercise simultaneously with this training film, because there is not enough time to assume the initial stance and exercises are shown only once (not repeated as it would be appropriate). As physical education teachers required a film suited to performing the exercise along with the instruction, so we introduced DVD2. Finally, we presented DVD3 for preschool and kindergarten teachers who had attended our course and wanted to see the adapted exercise program for younger children.

After a 9 year long continuous government support by January 2004, a total of 7772 physical education teachers teaching in 3715 schools had become familiar with the special posture correcting exercises. A total of 51475 functional muscle tests were conducted by the physical education teachers on 32831 students and revealed that only 11% of the children had the muscle balance necessary for supporting correct posture. In the remainder of the children, some or more posture supporting muscles were weakened and/or shortened[6].

The exercise program was included in the National Core Curriculum since 2003 within the physical education curriculum framework and made part of the qualification requirements for physical education teachers, as well as part of the objectives and actions of the National Public Health Program in 2001 and 2003. The National Core Curriculum, newly drafted in 2012, emphasizes to a much greater extent the necessity for posture correction (in addition to several other health promotion criteria). Though professional review (subject monitoring and supervision of subject matter), terminated in 1985, it has been reintroduced since 2012, in our experience physical education supervision has not paid adequate attention yet to the effective application of special posture correcting exercises. That is why health sector must take further steps.

The other objective of this preventive program was to achieve compulsory DPE – as this is the only way to reach all children.

Short-term and medium-term efficacy studies of the special posture correction exercises

The effectiveness of applying the special posture correction program integrated into formal physical education was tested several times.

A prospective controlled study was performed in the 2001/2002 school year on 6-14 years old students in Békéscsaba[13]. There were 200 students in the intervention group, and 213 in the control group. The postural muscles of the students were

Table 1. *Test Results of the Intervention (i=200) and Control (c=213) Groups*

Exercise number	1	2	3	4	5	6	7	8	9	10	11	12	Total
Fall-Interv.Grp.	1.62	1.52	1.68	1.32	1.59	1.32	1.52	1.43	1.29	1.59	1.4	1.45	17.76
Spring-Interv.Grp	1.49	1.03	1.19	1.04	1.28	1.13	1.36	1.29	1.1	1.42	1.24	1.33	14.93
Fall-Control Grp.	1.53	1.31	1.46	1.32	1.43	1.16	1.45	1.33	1.23	1.71	1.38	1.43	16.79
Spring-Control Grp.	1.7	1.21	1.44	1.35	1.32	1.12	1.53	1.29	1.27	1.83	1.39	1.54	17.03

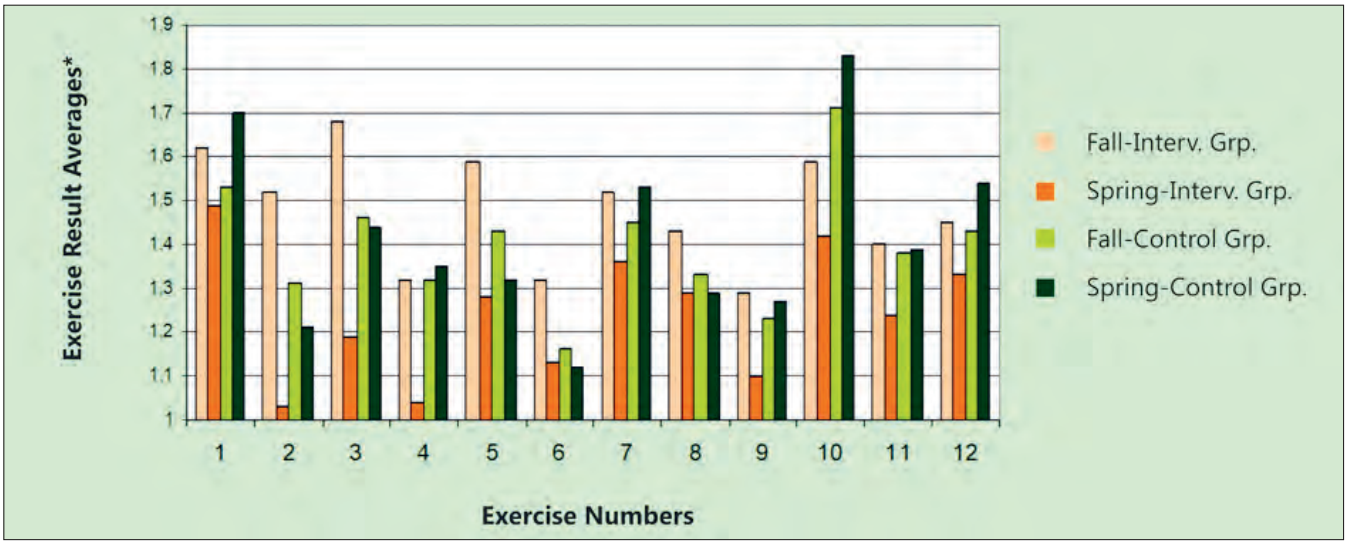

Figure 4. *Diagram of the Test Results of the Intervention (i=200) and Control (c=213) Groups*

*Correctly executed exercise = 1 point
Incorrectly executed exercise = 2 points

examined with the 12 test exercises from the posture correction program at the beginning and the end of the school year by an independent examiner (a well-practiced physiotherapist). The intervention group performed the posture-correcting exercises integrated into the regularly scheduled physical education classes under the direction of the teacher, while the control group had not performed these exercises. The controlled trial validated the efficacy of posture-correcting exercises integrated into physical education classes **(Table 1–3)**. **Table 1** and **Figure 4.** show the average results of the test exercises of both the Intervention and the Control Group. The one- and two-sample t-test results are summarized in **Table 2.** The one-sample t-tests of the Intervention Group show significant improvement ($p<0.01$) in each and every muscle test exercises while those in the Control Group showed significant deterioration ($p<0.01$) in 4 muscle test exercises by the end of the school years with 6 remaining unchanged and 2 (Nos. 2 and 5) showing significant improvement ($p<0.01$). The average total point of the 12 muscle test exercises showed significant improvement ($p<0.01$) in the Intervention Group and significant deterioration ($p<0.05$) in the Control Group. The two-sample t-tests showed a significant difference ($p< 0.01$) in the end of the year results between the Intervention Group and the Control Group (this applied also to all individual muscle tests and for their average total point). To understand the significant improvement shown by one-sample t-test of the No. 2 and 5 tests in the Control Group one has to look at the two-sample t-tests. These show that the improvement of the No. 2 and 5 tests in the Intervention Group was very significantly greater than that of the Control Group.

Chi-square distribution **(Table 3)** supports t-test results by showing that deterioration was seldom noted in those who regularly did the posture corrective exercises and significant improvement was much more likely, while among those who did not do the exercises, deterioration was much more likely, while improvement was seldom ($p< 0.01$).

A prospective study was performed to evaluate the effectiveness of applying special posture correcting exercises in Pásztó and in Szentgotthárd over

Table 2. *Controlled testing of the Hungarian Spine Society's Exercise Material: Summary table of t-test values*

Test Exercise Numbers	Intervention Group Results i=200 (one-sample t-tests)	Control Group Results c=213 (one-sample t-tests)	Changes in the Intervention Groups as compared to the Control Group (two-sample t-tests)
2, 5	Improved $p<0.01$	Improved $p<0.01$	Improved **$p<0.01$
1, 7, 10, 12	Improved $p<0.01$	Deteriorated $p<0.01$	Improved $p<0.01$
3, 4, 6, 8, 9, 11	Improved $p<0.01$	Unchanged	Improved $p<0.01$
Changes in average total point values *	Improved 17.76 → 14.93 $p<0.01$	Deteriorated 16.79 → 17.3 $p<0.05$	Improved 14.93 →← 17.03 $p<0.01$

*Best total point value = 12. Worst total point value = 24

**The degree of improvement noted in the Intervention Group is very significantly greater than that of the Control Group.

Table 3. *Controlled Testing of the Hungarian Spine Society's Exercise Material: Analysis of Chi-square distribution*

	Muscle Test showed improvement	Muscle Test showed no improvement	Total
No. of students who took part in the exercises	186	14	i = 200
No. of students who did not take part in the exercises	80	133	c = 213
Total	266	147	n = 413

$p < 0.01$
i = Number of students in Intervention Group
c = Number of students in Control Group
n = Total number of students tested

the 2009/2010 school year, involving 530 student, 7-12 years old, who performed the posture correction exercise program for 6 months integrated in physical education class, conducted by the teachers. Meanwhile, the condition of their postural muscles – evaluated with the 12 muscle tests – significantly improved ($p<0.01$ and $p<0.01$).

The Spinal Mouse is a small skin-surface device, exactly the size of a computer mouse (hence the name), connected to a computer. It is guided by hand along the spinal column along the spinosus processes, and the spinal curvature is analysed and presented graphically by the computer. According to this non-invasive spinal mouse computer-analysed examination, the rate of bad posture among participating student decreased from 64% (initial value) to 38.3% among students from Pásztó and from Szentgotthárd (Chi-square=16.6; degrees of freedom=3; $p=0.0009$). There was an inverse correlation between the students' muscle balance and body mass – that is, there was lower ratio for good postural balance among overweight students ($p<0.01$). Considering that obesity occurs more and more frequently among children and youth in our country, this is highly relevant. Trials in Pásztó and Szentgotthárd were part of the prevention arm of the Genodisc Research of the National Center for Spinal Disorders[6].

Tóthné Steinhausz et al. applied HSS's special posture-correcting exercises in kindergartens, they evaluated children with the 12 muscle test and a pressure sensor (pedograph) to measure and analyse pressure distribution on the feet. The condition of their postural muscles ($p=0.0001$) and the distribution's projection of the center of gravity ($p=0.002$) significantly improved[14].

Several physiotherapist students have written studies on the short-term efficacy of the HSS's program of special posture-correction exercises, though usually studying a small sample size. As every thesis supported the effectiveness, we have to aggregate results and analyze these in the future.

Evaluation of HHS's preventive program considering recently published international literature

Genodisc Research had presented not simply another scientific evidence of the high prevalence of incorrect posture and the effectiveness of special correcting exercises integrated in daily physical

education classes, but its objective evaluations of the spine before and after the exercise program – added to the semiobjective physical examination – was a novelty compared to our previous research[6].

The goal of the preventive program by HSS is supported also by recently published articles in leading journals. These authors highlighted again the tight biomechanical connection between the pelvis and the spinal column (sagittal balance) and emphasized the importance of biomechanically correct posture which would not overload the spinal structures[15–21]. The Prevention Program by the HSS is based on this evidence and helps to develop the correct posture.

The "European Guidelines for Prevention in Low Back Pain"[22] published in 2004 summarized recent reviews about the prevention of degenerative spinal disorders. Both the controlled trial in Békéscsaba and the prevention arm of the Genodisc study met the recommended main research focus: they were prospective, controlled trials with large sample sizes, intended to reduce the risks of low back pain in adulthood. It was only the requirement for long-term studies that our researches did not comply with, since the trials were not designed for long-term intervention follow-up. We have fulfilled the Guideline's requirement to appropriately influence decision makers as it is shown above.

In accordance with the Guideline's recommendations, the HSS's prevention program has influenced bio-psychosocial factors of low back pain in adults, because physical education teachers have several opportunities to influence not only the physical, but also the mental health of their.

The Guideline emphasizes the importance of researches lasting for several decades to support scientific evidence of the long-term effectiveness of preventive interventions in the reduction of bio-psychosocial risk factors. This would be a large-scale project, requiring financial resources and organization, so its realization is unlikely. Nonetheless, this is no excuse to ignore the application of already existing scientific evidences – as also the Guideline highlights.

We presented in 2013 a literature review on the primary prevention of symptoms of discopathy in the European Spine Journal[23]. The literature review shows that the HSS's preventive program is unique. Other preventive programs evaluated the short-term effect of interventions focused upon giving theoretical knowledge or upon a limited exercise routine to be performed during classes. In accordance with this experience, an analysis of physical education in the European countries provides an overview, in which it refers specifically to Hungary, where special posture correcting exercises are integrated in daily physical education classes[24].

Enhancing performance of posture correcting exercises in public education (2003-2021)

The subject of developing biomechanically correct posture has been part of National Core Curriculum and the physical education curriculum since 2003, and upon being reintroduced in 2012 then in 2019 it became more detailed. The training requirements for physical education teachers have included spine-specific joint protection since 2002. Since the start of the 2000s, the Institutes of Physical Education has taught the special posture correcting exercises based on cooperation with the HSS, but this subject was only optional – despite the training requirements. Even now whether it is a compulsory subject for every student seems to depend only on the institution's own approach.

The professional review terminated in 1985 and reintroduced in 2012, but is still not enough effective: it does not emphasize to a proper extent the necessity for posture correction (in addition to several other health promotion criteria). Apparently, the topic of the posture correction program has no place within the state-funded further training for teachers of physical education because of many other mandatory trainings in public education. Therefore the National Center for Spinal Disorders together with HSS shared the instruction book on the posture correcting exercises and three videos on its websites in 2014[11, 12], so these are now accessible for physical education teachers without taking part in special training course, and the website encourages physical education teachers themselves to practice precisely on their own bodies the posture correcting exercises before teaching them.

In 2014 – according to the wish of leading physical education teachers and with their contribution –, HSS created a table-form of the exercises to be applied in each physical education class. In every page the physical education teacher can see that special exercise which he has to apply in that special physical education class. So he can use this table-form easier than the booklet-form. As there are also graphs in it, one may understand the rough content of a page without knowing Hungarian. In 2021 this table was published also on the English version of the homepage of HSS[12].

The Hungarian School Sport Federation contributed to curricula developments in the field of physical education, where a new focus was given in

physical education on the criteria of health promotion, e.g. instead of the previously used fitness tests that often generated shear force in the lumbar spine, they developed a new fitness test battery (NETFIT[25]) which does not operate on shear force or do not harm the joints and the spine. Some of the HSS's muscle tests are also included in a measurable form. (About NETFIT see more in the supplementive part).

Conclusion

Posture-correction exercises that develop, automatize, and maintain biomechanically correct posture were strated by the HSS to integrate into daily physical education in 1995, and there were remarkable results. Yet, there are further activities to be performed.

First, it has to reach that special posture correcting exercises be a mandatory topic in the gradual training for all physical education teachers. For this purpose, the training requirements for physical education teachers must be better specified as a part of recent legislative amendments.

Second, posture-correction programs has to be part of the official post-gradual training for physical education teachers.

Third, it has to be reached that posture correction program's comprehensive inclusion be part of the training for subject monitoring and supervision specialists in relation to physical education.

Fourth, according to Government Decree No. 1177/2018 (XII.18), the National Musculoskeletal Program (author: Gyula Poór M.D., D.Sc.) including the National Preventive Center of Musculoskeletal Disorders and its national network has to be implemented. This means that, as part of the enhancing primary care, physiotherapists would work in outpatient settings and they would help and oversee the work for prevention in schools, too: they would teach posture correcting to physical education teachers, as well as assist them with the student examinations and follow-up work.

Fifth, school health services could help to better perform posture-correction exercises in DPE. Posture correction could be monitored by the school health servise using the Matthiass test[26], which is a semi-objective clinical test to detect postural muscle weakness. Based on the József Fodor School Health Society's three year pilot project examining the feasibility of the Matthiass test in practice[27], the Matthiass test is now planned to be integrated into the regular school health screenings as a recommended method.

Supplementum

DAILY PHYSICAL EDUCATION (DPE) AS PART OF HOLISTIC HEALTH PROMOTION (HHS) IN HUNGARIAN SCHOOLS

Because physical inactivity is one of the leading risk factors for noncommunicable diseases, the Global Strategy on Diet, Physical Activity an Health[28] states in 49.§: „Schools are encouraged to provide students with daily physical education." After several newer documents[29–34] the Physical Activity Strategy for the WHO European Region 2016-2025[35] highlights the need of at least 60 minutes physical activity daily for children and young people and recommends that schools should provide "an appropriate number of regular physical education lessons, in line with the available scientific evidence". Nationwide implementation of quality physical education classes and legislation are also recommended. Several facilitating factors were given from the international professional sites for holistic health promotion in schools, too: the lessons learnt from the European Network for Health Promoting Schools, now Schools for Health in Europe[36–38] and the supporting works of WHO European Region[39].

In Hungary - accordingly to the initiation of the HSS and with wide consensus of several medical societies - *DPE* was made an important goal of the National Public Health Program in 2001[40]. As the education sector was not convinced if schools were able to organize DPE, an intersectorial application for schools was organized in 2001 (Ministry of Health, Ministry of Education, Ministry of Sports). More than 700 schools applicated and this convinced the Ministry of Education that schools may organize DPE if they are given the missing financies. Thereafter DPE was included in the national education plan (2006), but DPE became part of the Government's Program only in 2010. The new *National Education Act Nr. 190 of 2011 prescribed DPE for all schools*, and after a 4 year long gradual implementation now all students take part in DPE since September 2015.

To achieve the expected health gains of DPE it must fulfill some special health-promoting criteria which were laid down together with several medical societies in 2012[6, 41–43] and these criteria of DPE became part of the basic ruling documents of public education in 2012. There were several big projects to enhance methodology of the PE teachers and the government is building gyms and swimming pools throughout the whole country to enhance quality of DPE, nevertheless physical education teacher's creativity is also needed for DPE classes

outside the gymnasium – as not the gym, but the physical activity is needed for all child every day.

The plan of HHP in schools was born in 2003, corresponding to the Parliamentary decision No. 46/2003. (IV.16.), and to the Public Health Interministerial Board's decisions the Ministry of Health in consensus with other competent departments (Ministry of Education, Ministry of Children, Youth and Sport, Ministry of Finance) created the plan of holistic health promotion (HHP) in schools, which – mainly because of lacking political commitment from the side of education – was not implemented until 2010.

In 2010 the Program of Government, in 2011 the Act Nr. 190 on National Education, and *in 2012 the Decree No. 20/2012 of the Minister for Education prescribed the institutionalized implementation of HHP* in all educational institutions. Since 2013 more projects from the health, the education and the sports sector gave significant professional assistance and motivation to schools to further their daily work in health promotion. An efficient intersectoral cooperation started and is still working on the basis of the Ministry of Human Capacities.

ESSENCE OF HHP

Holistic health promotion means a holistic, whole school approach where health promotion has to be part of the every day life of the school. There are four main health promoting tasks for schools to do in their daily work - with participation of the whole school, of parents and the public environment[43–45]:

I.) Healthy eating – potentially based on local food products;

II.) Daily physical education fulfilling health promotion criteria, and other forms of physical activity;

III.) Appropriate pedagogic methods (including also the use of arts) to enhance mental health;

IV.) Improving health literacy and health competencies of the children – topics see listed on the official website[44].

Effective implementation of HHP having so many beneficial consequences is considered a „whole society" target by the public health and the education administration as well. Therefore, in a joint effort the Secretariat of State for Education and the Secretariat of State for Health (Ministry of Human Capacities) issued in March 2016 the „Recommendation for every-day HHP activities of the pedagogues", listing all those websites where help would be available for them. The HHP Recommendation was mailed to all school leaders and was put on official websites. The Recommendation and legal tools to facilitate implementation of HHP in schools are available on the official website[44]. In February 2020 an online questionnaire was created and sent to all schools to ask them on how they can use the HHP Recommendation in their daily work. The results show that teachers and schools use many practical parts but they need further help from the health sector.

MONITORING OF DPE

Of the 4 basic health promoting tasks of HHP we have the best organized monitoring for the 2nd task: for DPE. HSSF in cooperation with the Cooper Institute (USA) created a new national measurement tool (NETFIT) for physical education teachers to monitor physical fitness of schoolchildren from 10 to 18 years old[40]. Online input of data and online analysis of results was made available for the public[25]. The devices for NETFIT were given to all Hungarian schools (more than 3800 schools). Since 2015 NETFIT is a yearly compulsory measurement for physical education teachers, for all 10-18 years old school-children, according to the Decree No. 20/2012 of the Ministry for Human Capacities. NETFIT has four profiles: body composition, aerob fitness, musculosceletal fitness and flexibility.

In May 2015 NETFIT was measured at the first time (623.026 schoolchildren took part with 13.543 teachers); in May 2016 it was measured on 651 431 school-children by 14.685 teachers and similarly it went on in the coming years. Main statements of the analysis after the first and second measurement are[25, 45]: 25,8% of children were overweight and obese, and this was worse than in 2015.

Worst results were seen in progressive aerobic capacity endurance test (PACER-test) – only 61,8% of the children were in health zone; in trunk lift test – only 51% of the children were in health zone. Developement of PACER test was detected first in 2016: girls developed in PACER-test by 10%, especially those who already have taken part in DPE.

According to the last measurements from May 2019 (in 2020 measurements were ceased because of COVID) it is seen that the PACER tests show further improvement even though physical education teachers have to work better: the results of PACER test are worsening with the age, obesity is slightly growing and trunk lift test is in every year the worst test among all tests of NETFIT[25].

NEEDED PROFESSIONAL HELP FROM THE PUBLIC HEALTH ACTORS FOR SCHOOLS IN THE FOUR TASKS OF HHP

As teachers are quite overloaded and their health literacy might be uncertain (as this is the case in the

Hungarian population), they cannot be left with their health promoting tasks alone. Many actors of the health system and of public health could and should give professional help to the schools in the following topics[45]:

Healthy eating – potentially based on local food products. Dieticians should go to schools and help them to reach children, parents and teachers working together so that children would like healthy diet.

Daily physical education fulfilling health promotion criteria and other forms of physical activity - physiotherapists should go to schools and help to the teachers of physical education so that they would learn and use posture correcting exercises more effectively.

Appropriate pedagogic methods (including also the use of arts) to enhance mental health - in this task health sector may help to find a good motivating tool for teachers so that they would change their old fashioned pedagogic methods to better ones and so they would enhance the mental health and wellbeing of their students and for themselves, also. Teachers should give more time for the use of arts in developing mental health, too.

Improving health literacy and health competencies of the children – in Hungary it is planned to develop an appropriate method for measuring health literacy of Hungarian school-children and adolescents for yearly countrywide use; this would be a big set (up to ca. 1000) of interesting online questions in all the important health themes, they would be entertaining and teaching in the same time.

The new quality management in education and the ongoing whole renewal of the national education are important helping structures and factors for HHP, e.g. all projects of the education sector are spreading the use of appropriate pedagogic methods to enhance mental health and wellbeing.

ACKNOWLEDGEMENT

I would like to say thanks to so many enthusiastic physiotherapists working in the prevention programme of the HSS - first of all to Zsuzsa Gardi, Artúrné Feszthammer, Irma Darabosné Tim, Viktória Tóthné Steinhausz, Ágnes Szilágyi, Sára Boja, and to Zsófia Horváth for helping in the translation into English. I am grateful to my boss, Péter Pál Varga M.D., funding director of the National Center for Spinal Diseases, for his continuous support and cooperation not only in the preventive work of the HSS but also in my struggle and work for HHP.

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B-SEJT-DEPLETIO A SCLEROSIS MULITPLEX TERÁPIÁJÁBAN: ÚJ SZEREPLŐ AZ OFATUMUMAB

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Hungarian https://doi.org/10.18071/isz.75.0163 www.elitmed.hu

Az elmúlt évek kutatási eredményei bizonyították, hogy a B-lymphocyták döntő szerepet játszanak a sclerosis multiplex (SM) patogenezisében. A betegség folyamatának jobb megértése a B-sejteket célzó antitest-terápiák kifejlesztését eredményezte, amelyek potenciális gyógyszerek lehetnek mind a relapszusos, mind a progresszív SM formáiban. A B-sejt-depletiós terápiák ezért mindinkább előtérbe kerülnek, és meghatározóak a betegség progressziójának csökkentésében. Az első B-sejt-depletáló, anti-CD20 monoklonális antitest a rituximab volt, amit sclerosis multiplexben is vizsgáltak, és a kedvező eredményeket követően újabb gyógyszerek kerültek kifejlesztésre, hasonló támadásponttal. 2017-ben az FDA, 2018-ban az EMA is engedélyezte egy másik anti-CD20 monoklonális antitest, az ocrelizumab relapszáló-remittáló sclerosis multiplex (RRSM) és primer progresszív sclerosis multiplex (PPSM) terápiájában történő bevezetését. Ez különösen jelentős előrelépés volt a PPSM kezelésében, hiszen ez volt az első gyógyszer, ami bizonyítottan csökkentette a progressziót PPSM-ben. A B-sejt-depletiós terápia új szereplőjeként nemrégiben lépett színre az ofatumumab, ami egy teljesen humán anti-CD20 monoklonális antitest. A gyógyszer alkalmazását 2021 márciusában az EMA is engedélyezte a sclerosis multiplex relapszáló formáiban (RSM). Összefoglalónkban részletesen bemutatjuk a jelenleg SM-ben alkalmazott anti-CD20 monoklonális antitest-terápiák hatásmechanizmusát és hatékonyságát.

Kulcsszavak: *sclerosis multiplex, anti-CD20 monoklonális antitest, ofatumumab, ocrelizumab, rituximab, B-sejt-depletio*

B-CELL DEPLETION IN THE THERAPY OF MULITPLE SCLEROSIS: OFATUMUMAB IS A NEW PLAYER

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Ideggyogy Sz 2022;75(5–6):163–169.

Research results in recent years have demonstrated that B-lymphocytes play a crucial role in the pathogenesis of multiple sclerosis (MS). The increased understanding of the disease process has resulted in the development of B cell-targeting antibodies as potential drugs for both relapsing and progressive forms of MS. Therefore, B-cell depletion therapies are becoming more prominent and determining in reducing disease progression. The first B-cell depleting anti-CD20 monoclonal antibody was rituximab, which has also been studied in MS and, following favourable results, new drugs have been developed with a similar point of attack. In 2017, the FDA and in 2018, the EMA approved ocrelizumab, another anti-CD20 monoclonal antibody, for the treatment of relapsing-remitting (RRMS) and primary progressive multiple sclerosis (PPMS). This was a particularly significant advance in the treatment of PPMS, as it was the first medication with a proven effect of reducing progression in PPMS. Ofatumumab, a fully human anti-CD20 monoclonal antibody, has emerged recently as a new player in B-cell depletion therapy. The drug has also recently been approved by the EMA in March 2021 for use in relapsing forms of MS. In this review, we detail the mechanism of action and efficacy of anti-CD20 therapies currently used in MS.

Keywords: *multiple sclerosis, anti-CD20 monoclonal antibody, ofatumumab, ocrelizumab, rituximab, B-cell depletion*

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Érkezett: 2021. december 16. Elfogadva: 2022. január 25.

A sclerosis multiplex (SM) elsősorban a fiatal korosztály (20–40 év) neurológiai betegsége. Epidemiológiai felmérések Magyarországon megközelítően 9000 beteget feltételeznek. A kórkép patomechanizmusában a neuroinflammatiós és a neurodegeneratív molekuláris mechanizmusok egyaránt jelen vannak, így a terápiának – farmakológiai támadáspontok szempontjából – igen széles körűek a lehetőségei. Remélhetőleg a potenciális gyógyszerek köre is tovább bővül a jövőben.

Újabb adatok a sclerosis multiplex patomechanizmusához

Az utóbbi évek kutatási eredményei megerősítették, hogy az SM-ben észlelt hosszú távú rokkantság nagyrészt független a relapszusoktól (progression independent relapse, PIRA), és jól korrelál az MR-felvételen talált agyi atrophiával[1]. *Haider* és munkatársai 30 éves periódust átfogó követéses eredményei ugyanis igazolták, hogy a kórkép igen korai fázisában (clinically isolated syndrome, CIS) mért agyi atrophia más faktoroktól függetlenül hosszú távon előre meghatározza a betegség progresszióját és a rokkantság mértékét[2]. Ide kívánkozik *Cree* és munkatársai[3] 138 betegen végzett vizsgálatának bemutatása. A páciensek közül 92 relapszáló-remittáló sclerosis multiplexesnek (RRSM) diagnosztizált betegnél „rejtett állapotrosszabbodást" (silent progression, SP) találtak, ami minden bizonnyal az RRSM-ben zajló neurodegeneratív folyamattal lehet összefüggésben. Ezen adatok ismeretében valószínű, hogy a szekunder progresszív sclerosis multiplexben (SPSM) zajló celluláris/molekuláris történések jóval korábban jelen vannak, mint ahogy azt feltételezzük. Felvetődött a betegség megközelítésének olyan szemlélete is, hogy az SM valójában primer progresszív betegség, s a betegek egy részénél relapszusok is jelen vannak[4]. Az elmúlt évek kutatási eredményei bizonyították, hogy a B-lymphocyták döntő szerepet játszanak az SM patogenezisében, ezért a B-sejt-depletiós terápiák mindinkább előtérbe kerülnek, és meghatározóak a betegség progressziójának csökkentésében[5]. Ezek az újabb adatok kritikus fontosságúnak bizonyulnak a klinikai döntéshozatalban, különösen a gyógyszeres kezelésben. A közelmúltban bevezetésre kerültek olyan B-sejt-depletáló farmakonok, amik az SM relapszáló klinikai megjelenéseiben (CIS-ben, RRSM-ben és aktivitással járó SPSM-ben) és a primer progresszív formában (PPSM) egyaránt alkalmazhatók. A következő fejezetben arra keressük a választ, hogy a B-sejteknek – az immunglobulin szintézise mellett – lehet-e „direkt" szerepük az idegszövet károsodásában?

Mi a szerepe a B-sejteknek az idegszövet károsodásában?

A B-sejtekre ható terápiák sikeressége más megvilágításba helyezte az SM patomechanizmusáról alkotott képünket. Már a múlt század 40-es éveiben igazolták, hogy az SM-betegek liquorában növekedett az immunglobulin koncentrációja, így a B-sejtek szerepe az SM patomechanizmusában a neuroimmunológia részletesen vizsgált területe lett. Az oligoclonalis IgG-csíkok a betegek nagy részénél detektálhatók. A B-sejtekből képződő érett plazmasejtek ellenanyagot termelnek, és kiváltják az SM-ben több mint 90–95%-ban előforduló oligoclonalis gammopathiát (OGP)[5]. Antigénspecifikus memória-B-sejtek szintén jelen vannak a betegek központi idegrendszerében, és kimutathatók az SM-es elváltozásokban[6]. Ez, valamint az a tény, hogy az SM-laesiókban antitest- és komplementdepozíciók vannak, továbbá bizonyított az antigén kiváltotta klonális B-sejt-expanzió is a központi idegrendszerben (KIR)[7], együttesen arra utalnak, hogy a B-sejtek a KIR-i antigénekre specifikus autoantitestek termelésével hozzájárulhatnak az SM patológiájához[5].

A B-sejtek azonban antitesthatásuktól függetlenül is közrejátszhatnak az idegszövet átmeneti vagy tartós károsodásában. Képesek ugyanis antigént prezentálni a T-sejteknek, és proinflammatorikus [IL-6, IL-12, IL-15, TNF-α, IFN-γ, granulocyta-macrophag kolóniastimuláló faktor (GM-CSF)], valamint antiinflammatorikus citokineket felszabadítani, melyek regulálják az immunfolyamatokat[8]. SM-betegek perifériás vérében abnormális B-sejt-citokin egyensúlyt figyeltek meg a gyulladásos és proinflammatoros citokinek, valamint az antigénprezentációs kapacitás között[5]. Ez az aberráns citokinprofil vélhetően hozzájárul a kóros T-sejtválaszhoz SM-ben, és a B-sejt-depletio terápiás hatásának hátterében is ez állhat[9]. Emellett a B-sejtekben gazdag meninxben leírt follikulusszerű struktúrák (follicle-like structure, FLS) alapján valószínű, hogy a betegség progresszív fázisában is komoly szerepük lehet. SM-ben B-sejtekben gazdag FLS-eket mutattak ki az agyhártyában (SPSM-ben gyakoribb volt az előfordulásuk), aminek alapját a subpialis corticalis károsodás képezi[10–12]. Az ilyen FLS-ek megjelenése a betegség korábbi kezdetével és progresszívebb lefolyásával áll összefüggésben. Az agykérgi neuronvesztés mértéke is arra utal, hogy az ezekből a struktúrákból felszabaduló szolúbilis faktoroknak kóroki szerepe van az SM progresszív fázisában[10]. A KIR-ben a patológiás folyamatok kompartmentalizációját is megfigyelték az SM progressziójával kapcsolatban[8]. *Lisak* és

munkatársai *in vitro* vizsgálata igazolta, hogy a B-sejtek citotoxikus hatást fejtenek ki *in vitro* oligodendroglia-tenyészeten, ami a demyelinisatio egyik faktora lehet[13]. Megemlítendő azonban, hogy a B-sejtekből generált immunglobulinok nem feltétlenül reagálnak az agyszövetben lévő myelinproteinnel[5, 14], ezért az SM-betegek központi idegrendszerében termelődő immunglobulinok patogenitása továbbra is bizonytalan.

A B-sejtek tehát számos mechanizmus révén hozzájárulhatnak az SM patogeneziséhez és az idegszövet károsodásához, beleértve 1. az antitesttermelést, 2. az antigénprezentációt, 3. a T-sejtválasz modulációját, ideértve 4. az autoproliferatív CD4+ T-sejtek aktiválását és proliferációját a KIR-be, 5. a proinflammatorikus citokin- és kemokintermelést, valamint 6. a patológiás folyamatok kompartmentalizációját. Következésképpen megállapítható, hogy a B-sejteknek fontos szerepük van az SM kialakulásában és progressziójában a különböző antitestfüggő és -független hatások révén[5].

B-sejteket depletáló farmakonok

Az SM legtöbb terápiája a T-sejtek aktiválását, e sejtek KIR-be való bejutását és a lymphocyták effektor funkcióit célozza, de e terápiák közül sok egyidejűleg a B-sejtekre is hat. A patogenetikai bizonyítékok figyelembevételével a közelmúltban egyre több specifikus B-sejt-ellenes gyógyszert fejlesztettek ki és teszteltek az SM kezelésére, különböző stratégiákat alkalmazva, eltérő eredményekkel.

A B-sejtek számos celluláris markerrel azonosíthatók, ami lehetővé teszi további alcsoportok differenciálását, valamint ezekkel a markerekkel a sejtek az érés és differenciálódás szinte minden stádiumában azonosíthatók. Ilyen celluláris marker a transzmembrán fehérje CD20, ami jelentős mértékben expresszálódik a B-sejtek felszínén, és fontos szerepet játszik azok plazmasejtté való differenciálódásában, valamint az antigénindependens T-sejt-válaszok aktiválásában. A CD20 nem expresszálódik az őssejteken, a pro-B sejteken és a plazmasejteken, de megtalálható a pre-B-sejteken, a naiv B-sejteken és a memóriasejteken is[15, 16]. A CD20 monoklonális antitestekkel való szelektív megcélzásával az utóbbi években lehetségessé vált a B-sejtek depletálása. Ismert tény, hogy az anti-CD20 monoklonális antitestek komplementmediált lysis (CDC), illetve antitestdependens celluláris citotoxicitás (ADCC) és apoptózis révén elpusztítják a CD20-t hordozó B-sejteket[15]. Megjegyezzük, hagyományosan azt gondolták, hogy a CD20 kizárólag B-sejtes marker. Korábbi vizsgálatok során azonosították a T-sejtek kis alcsoportjánál is, azonban tisztázatlan, hogy depletiójuk felelős-e az anti-CD20-terápiák bizonyos hatásaiért[17]. A CD20 megcélzása monoklonális antitestekkel forradalminak bizonyult a B-sejtes leukaemiák és lymphomák ellen, valamint újabban az olyan autoimmun betegségek ellen is, amelyekben a B-sejtek alapvető szerepet játszanak (ilyen a szisztémás lupus erythematosus és az SM)[15, 18].

A közelmúltban átfogó klinikai vizsgálatok bizonyították az anti-CD20 antitestekkel végzett B-sejt-depletiós terápia hatékonyságát mind a relapszussal járó, mind a progresszív SM-ben. A B-sejt-depletiós terápiákkal végzett vizsgálatokat SM-ben azon feltételezés mentén indították, hogy azok a patogén antitestek mennyiségének csökkentésén keresztül fejtik ki hatásukat. Az eredmények azonban azt bizonyítják, hogy farmakológiai hatásuk az antitestszintek jelentős befolyásolása nélkül alakul ki. Egyre több bizonyíték utal arra, hogy az anti-CD20 monoklonális antitestek a B-sejt-depletio következtében kialakuló T-sejt-aktivitás modulációján keresztül csökkentik az SM aktivitását[5]. A kezdeti várakozásokkal ellentétben tehát a B-sejt-depletio fő terápiás mechanizmusa **(1. ábra)** SM-ben valószínűleg nem az autoantitestek csökkentésén, hanem az aberráns citokinprofilú és antigénprezentáló képességű B-sejtek depletióján alapul, ami az abnormális autoreaktív T-sejt-válaszok szuppresszióját eredményezi[5].

Az elmúlt években számos B-sejt-ellenes gyógyszert fejlesztettek ki az SM kezelésére. A jelenleg klinikai gyakorlatban alkalmazott, anti-CD20 monoklonális antitestekkel végzett B-sejt-depletiós terápiák hatásmechanizmusát és hatékonyságát az alábbiakban részletezzük.

RITUXIMAB

A rituximab egy egér-humán kiméra anti-CD20 monoklonális IgG1 antitest, ami a B-sejteket a komplementfüggő citotoxicitás révén depletálja. Ugyanakkor az antitestfüggő sejt mediálta citotoxicitás is lényeges eleme a farmakon hatásának[19]. Meg kell továbbá említeni, hogy a rituximab apoptózist is képes indukálni a B-sejtekbe történő kalciumion-beáramlás fokozása révén[20].

A HERMES vizsgálatban a rituximab egyszeri intravénás adását követően 91%-kal csökkent a kontraszthalmozó laesiók száma (MR-aktivitás)[21]. Egy II/III. fázisú, kettős vak, multicentrikus vizsgálat (OLYMPUS) eredményei nem voltak meggyőzőek PPSM-betegek esetében. A vizsgálat nem érte el az elsődleges végpontját, mivel a rituximabnak nem volt statisztikailag szignifikáns hatása a beteg-

1. ábra. *B-sejt-depletio terápiás mechanizmusa SM-ben. Kezeletlen SM-ben a B-sejtek proinflammatorikus citokinek (IFN-γ és az IL-17) termelését facilitálják a T-sejteken keresztül. A kóros T-sejt-válasz alapja a B-sejtek abnormális citokinegyensúlya. A B-sejt-depletio (középen) csökkent T-sejt-aktivitást okoz. A B-sejt-depletio után újra megjelenő B-sejtek (repopuláció) már csökkent proinflammatorikus (TNF-α, LT, IL-6, GM-CSF) és fokozott gyulladáscsökkentő citokinprofillal (IL-10) rendelkeznek, ami a T-sejt-aktivitás szuppresszióját eredményezi (5)*

TNF-α: tumornekrózis-faktor-alfa, LT: lymphotoxin, IL: interleukin, GM-CSF: granulocyta-macrophag kolóniastimuláló faktor, IFN-γ: interferon-gamma

ség progressziójának lassításában. Az alcsoportelemzés azonban azt mutatta, hogy a fiatalabb (<51 éves) és az MR-en gadolíniumhalmozást mutató laesiókkal rendelkező betegek számára előnyös volt a rituximabkezelés[22]. Vizsgálták még a rituximab intrathecalis adását SPSM-betegeknél, mivel egyre több bizonyíték látott napvilágot, hogy a KIR-en belüli B-sejtek aktivitása összefügg a betegség progressziójával. A RIVITaLISe vizsgálatot – amelyben a rituximab egyidejű intravénás és intrathecalis adagolását vizsgálták – azonban idő előtt befejezték. Az előre meghatározott, különböző biomarkereket [köztük a neurofilamentum könnyűlánc-fehérje (sNfL)] vizsgáló időközi elemzés nem bizonyította a hatékonyságot. A tanulmány szerint a rituximab intrathecalis adása a liquorban lévő B-sejtek depletióját eredményezte, azonban a hatás átmeneti volt, és a KIR-ben lévő B-sejtek nem depletálódtak hatékonyan[5]. Noha a rituximab jelenleg nem engedélyezett az SM kezelésében, *„off-label”* terápiaként jó néhány európai országban alkalmazzák.

OCRELIZUMAB

Az ocrelizumab humanizált anti-CD20 IgG1 monoklonális antitest. SM-ben kifejtett terápiás hatásmechanizmusa nem teljesen ismert, de feltételezhetően szerepet játszik benne az immunmoduláció a CD20-expresszáló B-sejtek számának és funkciójának csökkentésén keresztül. A B-sejt-depletiót a sejtfelszínhez történő kötődést követően nagyrészt antitestfüggő celluláris phagocytosis (ADCP) révén idézi elő[19], de antitestfüggő celluláris citotoxicitás, komplementfüggő citotoxicitás és apoptózis útján is szelektíven depletálja a CD20-expresszáló B-sejteket[8]. A rituximabhoz képest nagyobb ellenanyag-mediált és sejtmediált hatással, valamint csökkent komplementfüggő citotoxikus hatással bír. A humanizált ellenanyag kevésbé immunogén, így kedvezőbb haszon-kockázat profillal rendelkezhet, mint a rituximab[8]. Az ocrelizumab mind a relapszáló, mind a primer progresszív kórformában hatásosnak bizonyult. Kiemelendő, hogy az OPERA I/II (randomizált, multicentrikus, kettős vak és kettős placebós) klinikai vizsgálatban az ocrelizumab az interferon-β-1a-val összehasonlítva jelentősen csökkentette (OPERA I: 46%, OPERA II: 47%) az éves relapszusrátát, valamint szignifikánsan csökkent az MR-aktivitás is[23]. A betegek mintegy 50%-a teljesítette a NEDA-3 kritériumait. PPSM-betegeknél az ORATORIO vizsgálatban az ocrelizumab csökkentette az EDSS-ben (Expanded Disability Status Scale, kiterjesztett rokkantsági állapot skála) mért progressziót és az új vagy növekvő T2-laesiók számát is[24]. A fenti adatok alapján az FDA 2017 márciusában, míg az EMA 2018. januárban engedélyezte a gyógyszer bevezetését az SM-terápiában.

OFATUMUMAB

Az ofatumumab egy teljesen humanizált anti-CD20 IgG1 monoklonális antitest. Pontos hatásmechanizmusa az SM kezelésében nem teljesen tisztázott. A pre-B- és az érett B-lymphocyták CD20 antigénjéhez kötődve antitestdependens sejt mediálta cito-

1. táblázat. *Ofatumumab: a randomizált klinikai vizsgálatok jellemzői, kimenetele*

Szerző	Résztvevők	A vizsgálat felépítése	Klinikai végpont, eredmények	MR-végpont, eredmények
Sorensen és munkatársai, 2014[25]	38 RRSM-beteg	48 hetes, II. fázisú, kettős vak, randomizált, placebokontrollált vizsgálat	Csökkent relapszus-előfordulás placebóval szemben (19% vs. 25%)	Új és megnagyobbodott T1 és T2 gadolíniumhalmozó agyi laesiók száma csökkent
Bar-Or és munkatársai, 2014[26]	231 RRSM-beteg	48 hetes, II. fázisú, kettős vak, randomizált, placebokontrollált vizsgálat (MIRROR)	Nincs	Dózisfüggő csökkenés a gadolíniumhalmozó laesiók számában
Hauser és munkatársai, 2020[27]	1882 RRSM-beteg	III. fázisú, kettős vak, randomizált, placebokontrollált vizsgálat (ASCLEPIOS I & II). Aktív komparátor a teriflunomid.	Csökkentette az éves relapszusrátát (egyikben 50,5%-kal, a másikban 58,5%-kal), valamint a 3 hónapos igazolt funkcióromláshoz vezető progressziót (confirmed disability progression, CDP) 34,4%-kal mérsékelte, míg a 6 hónapos CDP kockázatát 32,5%-kal csökkentette a teriflunomiddal összehasonlítva.	Erőteljes csökkenés a T1 és T2 gadolíniumhalmozó laesiók számában

RRSM: relapszáló-remittáló sclerosis mutliplex

toxicitást és komplementmediált lysist eredményez, aminek hatására a gyógyszer alkalmazásának első két hetét követően a betegek 95%-ánál a B-sejtek száma a normál alsó határérték alá csökkent. A sejtlysis mechanizmusa hasonló az ocrelizumabéhoz, habár az ofatumumab több CDC-t okoz, mint ADCC-t[16].

Az ofatumumab SM-kezelésben betöltött szerepét több vizsgálatban is értékelték **(1. táblázat)**. Egy kis méretű, II. fázisú, kettős vak, randomizált, placebokontrollos vizsgálatban 38 RRSM-beteg kapott intravénás ofatumumabot vagy placebót kéthetes időközönként. Egy 26 betegből álló csoport kéthetente 100, 300 és 700 mg ofatumumabot kapott, míg a fennmaradó 12 beteg placebokezelésben részesült. 24 hét elteltével felcserélték a két kezelési kart, és az addig placebót kapó résztvevők ofatumumabot kaptak. 24 hetes ofatumumabkezelés után az MR-en látható új T1 és T2 gadolíniumhalmozó agyi laesiók aktivitásának 99%-os csökkenéséről számoltak be. A teljes szérum-IgG tekintetében nem volt csökkenés megfigyelhető, az ofatumumabot a betegek jól tolerálták[25].

Egy másik, II. fázisú, 48 hetes, kettős vak, placebokontrollos, randomizált és a gyártó által szponzorált, MIRROR elnevezésű vizsgálatot végeztek a subcutan ofatumumab vizsgálatára placebóhoz képest, 231 RRSM-beteg körében[26]. A vizsgálatban az ofatumumab szignifikánsan csökkentette az új gadolíniumhalmozó agyi laesiók számát.

Ezt követően két III. fázisú vizsgálat során is értékelték az ofatumumab hatásosságát és biztonságosságát, összehasonlítva a teriflunomid aktív komparátor készítménnyel SM-ben[27]. Az ASCLEPIOS I és II randomizált, kettős vak, párhuzamos csoportos vizsgálatokba összesen több mint 1800 RSM-beteget vontak be. Az elsődleges végpont mindkét esetben az éves relapszusráta volt 2,5 év időtartamot figyelembe véve. A másodlagos végpontok között az EDSS-skálán 3 és 6 hónap alatt bekövetkező javulás, illetve romlás, az MR-vizsgálatok során észlelhető új vagy növekvő számú kontraszthalmozó T1- és T2-laesiók száma, valamint az sNfL koncentrációja szerepelt. Mindkét vizsgálatban ugyanaz az eredmény született: az ofatumumab a teriflunomidhoz képest szignifikánsan csökkentette az éves relapszusrátát (egyikben 50,5%-kal, a másikban 58,5%-kal). Az ofatumumabbal végzett kezelés a gadolíniumhalmozó T1 agyi laesiók számának erőteljes (95,9%-kal) csökkenésével és az új vagy növekvő T2-laesiók arányának jelentős (83,5%-kal) csökkenésével járt az MR-en. Az ofatumumab a teriflunomiddal összehasonlítva a 3 hónapos igazolt funkcióromláshoz vezető progressziót (confirmed disability worsening, CDW) 34,4%-kal mérsékelte, míg a 6 hónapos CDW kockázatát 32,5%-kal csök-

kentette. Megemlítendő továbbá, hogy az ofatumumabbal kezelt betegeknél az sNfL szintje a 3. hónaptól kezdődően jelentősen csökkent a teriflunomiddal kezelt betegekhez képest.[27] Az ofatumumab növelte a NEDA-3 elérésének valószínűségét, és a teriflunomiddal szemben jobb hatékonyságot mutatott az RSM-betegeknél. A kezelés első évében 10 betegből majdnem 5, míg a kezelés második évében 10 betegből közel 9 elérte a NEDA-3 értéket[28].

Az ofatumumab alkalmazását az FDA 2020 augusztusában, az EMA 2021 márciusában engedélyezte az SM relapszáló formáinak kezelésében. A gyógyszer figyelemreméltó előnye, hogy a világ első olyan B-sejt-depletiós terápiája, amit az SM-betegek önmaguknak adagolhatnak. Az ofatumumab további előnye, hogy négyhetente egyszer kell alkalmazni, és subcutan adagolható a beteg vagy a gondozó által egy automata injekciós toll segítségével, ami lényegesen kisebb terhet ró az ellátó személyzetre. Megemlítendő továbbá, hogy az alkalmazási előírás alapján a szülést követő néhány nap múlva az ofatumumab szoptatás közben is alkalmazható, amennyiben azt a kezelőorvos szükségesnek tartja.

Mit igazol a hálózati metaanalízis az ofatumumab terápiás indikációjával kapcsolatban?

Felmerül a kérdés, hogy hol helyezkedik el az ofatumumab az SM terápiájában a jelenleg alkalmazható gyógyszerek között? Az ECTRIMS-EAN 2018-ban közzétett közös iránymutatása az RRSM-ben az alábbi farmakonok alkalmazását javasolja (ABC-sorrendben): alemtuzumab, cladribin, daclizumab (biztonságossági megfontolásból kivonták), dimetil-fumarát, fingolimod, glatiramer-acetát, IFN-β-1a, IFN-β-1b, natalizumab, ocrelizumab, peginterferon-β-1a és teriflunomid[29].

Az egyes farmakonok között összehasonlító klinikai vizsgálatok korlátozottan történtek, ezért hálózati metaanalízis módszerrel vizsgálták az ofatumumab helyét az SM terápiás gyógyszerpalettáján. Az analízis azt igazolta, hogy a subcutan alkalmazott ofatumumab valószínűleg hasonló effektivitású, mint például az alemtuzumab, a natalizumab vagy az ocrelizumab. Megemlítendő, hogy a többi farmakonnal összehasonlítva az ofatumumab egyes esetekben a relapszusráta csökkenésében és a rokkantság progressziójának lassításában hatásosabbnak bizonyult vagy hatása statisztikailag nem különbözött[30].

Záró gondolatok

Az SM területén tapasztalt töretlen kutatási lelkesedésnek köszönhetően egyre több ismeret áll rendelkezésünkre a betegség patomechanizmusáról, amiből a gyógyszerfejlesztés is nagyban profitál. Bár a B-sejtek szerepe az SM patogenezisében egyértelmű, még mindig sok a megválaszolatlan kérdés. Nem teljesen tisztázott, hogy milyen tényezők játszanak szerepet a KIR-be való bejutásukban, milyen mechanizmusok révén jutnak át a vér-agy gáton, valamint milyen szerepük van a betegség progressziójában.

E megválaszolatlan kérdések ellenére a B-sejtek depletióját célzó terápiák sikere és a közelmúltbeli klinikai vizsgálatok eredményei segítették és megerősítették az SM patofiziológiájának modern megértését, ami szerint az SM mind a T-, mind a B-sejtek betegsége.

A rendelkezésre álló evidenciák alapján egyre bizonyosabb, hogy – a korábbi paradigmákkal ellentétben – az eszkalációs kezelés helyett a nagy hatásosságú gyógyszerek korai bevezetése mindinkább teret hódít az aktív relapszáló SM-betegeknél. A B-sejt-depletiós terápiákat a betegség kezdetén alkalmazva kiváló eredmények érhetők el a kór hosszú távú lefolyásában, és akár éveken át tartó, betegségaktivitástól mentes időszakról is beszélhetünk.

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REM SLEEP, REM PARASOMNIAS, REM SLEEP BEHAVIOUR DISORDER

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English https://doi.org/10.18071/isz.75.0171 www.elitmed.hu

We review the literature on REM parasomnias, and their the underlying mechanisms. Several REM parasomnias are consistent with sleep dissociations, where certain elements of the REM sleep pattern emerge in an inadequate time (sleep paralysis, hypnagogic hallucinations and cataplexy) or are absent/partial in their normal REM sleep time (REM sleep without atonia, underlying REM sleep behavior disorder). The rest of REM parasomnias (sleep related painful erection, catathrenia) may have other still unclear mechanisms.
REM parasomnias deserve attention, because in addition to disturbing sleep and causing injuries, they may shed light on REM sleep functions as well as the heterogeneous etiologies of parasomnias. One of them, REM sleep behavior disorder has special importance as a warning sign of evolving neurodegenerative conditions mainly synucleinopathies (some cases synucleinopathies themselves) and it is a model parasomnia revealing that parasomnias may have by autoimmune, iatrogenic and even psychosomatic etiologies.

Keywords: *REM sleep, REM parasomnia, REM sleep behavior disorder, synucleinopathy*

REM-ALVÁS, REM-PARASOMNIÁK, REM-MAGATARTÁSZAVAR
Szűcs A, MD; Mutti C, MD; Papp A, MD; Halász P, MD, PhD; Parrino L, MD
Ideggyogy Sz 2022;75(5–6):171–182.

Áttekintjük a REM-parasomniák irodalmát, és röviden foglalkozunk a hátterükben álló mechanizmussal. A csoport tagjainak egy része alvásdisszociációnak felel meg, ahol a REM-alvás egyes elemei inadekvát fázisban (például alvási paralysis, hypnagog hallucinációk) jelennek meg, vagy fordítva, elmaradnak/töredékesek a REM-alvás alatt, amelynek egyébként fiziológiás részei (REM-alvás izomatónia nélkül, a REM-magatartászavar hátterében álló rendellenesség).
A többi REM-parasomnia (alvásfüggő fájdalmas erectio, catathrenia) hátterében egyéb, egyelőre tisztázatlan mechanizmus állhat. A REM-parasomniák alvászavart és sérüléseket okozhatnak, és tanulmányozásuk megvilágíthatja a REM-alvás funkcióit és a parasomniák hátterében álló sokszínű etiológiát. A REM-magatartászavarnak különleges jelentősége van: neurodegeneratív betegségek, különösen synucleinopathiák előjele (vagy kísérője) lehet, talán maga is az. Egyben modell-rendellenesség, ami autoimmun, iatrogén és pszichoszomatikus zavarok feltárását teheti lehetővé.

Kulcsszavak: *REM-alvás, REM-parasomnia, REM-magatartászavar, synucleinopathia*

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Érkezett: 2021. június 24. Elfogadva: 2021. szeptember 26.

The International Classification of Sleep Disorders (2014) defines parasomnias as unusual movements, behaviors, autonomic phenomena and dreams during sleep. They may co-occur with other sleep disorders e.g. obstructive sleep apnea syndrome, other parasomnias or epilepsy[1]. Based on the hosting sleep stage, NREM-, REM-sleep-related and other parasomnias are distinguished. We overview REM parasomnias focusing on REM sleep behavior disorder (RBD).

Physiology background

Sleep, regulated by intrinsic rhythm-generators and environmental stimuli, is far from homogeneous. It is composed of the cyclic alternation of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages constituting the macrostructure of sleep. Both REM and NREM sleep are under homeostatic control[2]. REM sleep alternates phasic and tonic phases[3, 4] while NREM sleep contains multi-level oscillations as the cyclic alternating pattern (CAP), the alternation of slow wave up- and down states and possibly shorter rhythms[5].

The pattern of REM sleep is made by the combination of striated muscle atonia, rapid eye movements, dreaming, a desynchronized EEG activity, "saw tooth" waves (STW), ponto-geniculo-occipital (PGO) discharges and rhythmic hippocampal slow waves[6].

The GABAergic inhibitory neurons in the dorsomedial medulla (DmM) and the excitatory neurons in the ventral medulla (VM; containing the GABA synthesizing enzyme, glutamate decarboxylase - GAD2) initiate and maintain REM sleep, possibly through their projections to the dorsal and median raphe (DR; MR). During NREM sleep, their activity synchronizes with the infraslow oscillations of the EEG spindle band, modulating the latency of REM sleep episodes. Thus, dorsomedial and ventral medullary neurons promote REM sleep, and their slow activity-changes may coordinate NREM-REM sleep transitions[7].

STW are theta-range transients emerging from the EEG background. They are joined by an increase of variable frequency oscillations over widespread cortical regions, suggesting an involvement in cognitive processes[8].

PGO waves are biphasic field potentials known in several mammalians including humans[9]. Pontine P-waves (parts of PGO waves) couple with hippocampal slow oscillations – theta in mice, delta in humans. Together with the bursts of hippocampal CA1 neurons, they may coordinate brainstem and hippocampal activity and participate in sleep-related neural plasticity[10, 11].

A recent revolutionary discovery has identified Gq-type muscarinic acetylcholine receptors (Chrm) 1 and 3 as 'dream genes'; their knock-out resulted in short-sleeper phenotypes and loss of REM sleep[12, 13].

PHASIC AND TONIC REM

Phasic REM sleep features muscle twitches, rapid eye movements, PGO waves and dreaming. In tonic REM sleep with even EEG activity, the awakening threshold is lower and the evoked responses resemble those in waking[3, 14].

THE REM SLEEP NETWORK

Jouvet's pioneer cat-brain trans-section experiments[15] have shown that the neural circuitry of REM sleep nestles in the brainstem, mainly in the

ABBREVIATIONS

BDNF: brain-derived neurotrophic factor
CA: cornu ammonis
CAP: cyclic alternating pattern
Chrm: muscarinic acetylcholine receptor
CeA: central amygdala
cLDTN: caudal laterodorsal tegmental nucleus
DLB: diffuse Lewy body disease
DmM: dorsomedial medulla
DR: dorsal raphe
DTI: diffusion tensor imaging
EEG: electroencephalography
EMG: electromyography
GABA: γ-aminobutyric acid
HLA: human leucocyte antigen
LC: locus coeruleus
LH: lateral hypothalamic
LDT: laterodorsal tegmental (pontin)
LPT: lateral pontine tegmental
MCH: melanin-concentrating hormone
MN: motoneuron
MR: median raphe
MRI: magnetic resonance imaging
NREM: non-REM
OX: orexin
PC: precoeruleus
PD: Parkinson's disease
PGO: ponto-geniculo-occipital
PPT: pedunculo-pontin-tegmental
RBD: REM sleep behaviour disorder
REM: REM rapid eye movement
RSWA: REM sleep without atonia
SLD: sublaterodorsal
SSRI: selective serotonin reuptake inhibitor
SSNI: selective noradrenaline reuptake inhibitor
STW: saw tooth wave
SVH: spinal ventral horn
TDP-43: transactive response DNA 43 kDA binding protein
vlPAG: ventro-lateral periaqueductal grey
VM: ventral medulla
VmM: ventromedial medulla

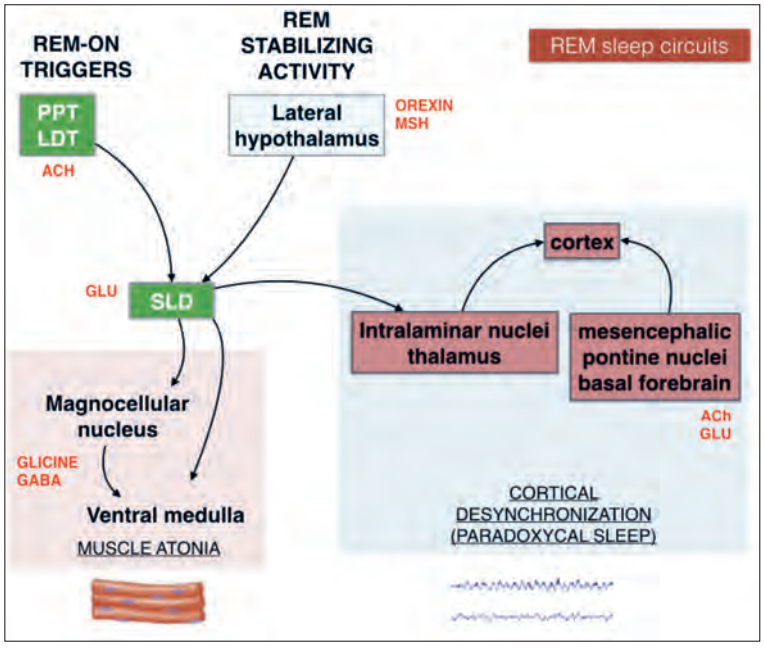

Figure 1. *REM sleep network. The caudal laterodorsal tegmental nucleus (cLDT), the sublaterodorsal (SLD) nucleus and precoeruleus region (PC) comprise an executive pontine circuit element for REM sleep. REM-on glutamatergic neurons of the ventral SLD mediate REM motor atonia through direct synaptic activation of glycinergic interneurons of the spinal ventral horn (SVH) as well as via GABAergic/glycinergic neurons of the ventromedial medulla (VmM). Lateral hypothalamic neurons containing orexin (OX) provide excitatory and stabilizing synaptic control over LPT neurons. Cholinergic laterodorsal tegmental and pedunculopontine tegmental (LDT/PPT) neurons may produce REM sleep through activation of REM-on SLD neurons. Lateral hypothalamic (LH) neurons containing melanin-concentrating hormone (MCH) also regulate REM sleep, possibly through direct inhibition of REM-off vlPAG/LPT neurons*[20]

dorso-rostral pons. A REM on/off system regulates REM through multiple ascending and descending sleep trajectories[16] **(Figure 1)**.

The rise of ACh from laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) neurons promotes REM sleep through the activation of REM-on glutamatergic sublaterodorsal (SLD) neurons[2]. REM-on neurons' activation (and concomitant REM-off circuits' inhibition) is supported by the suspension of the tonic monoaminergic and GABAergic inhibition present in wakefulness and slow-wave sleep. SLD activity builds up the REM sleep pattern throughout descending inhibitory signals generating muscle atonia and ascending activating pathways leading to cortical desynchronization.

The melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus have maximal activity during REM-sleep regulating it by the inhibition of the REM-off GABAergic, histaminergic and mono-aminergic neurons[17, 18]. Also the orexin neurons of the lateral hypothalamus stabilize REM sleep through their receptors on 3/4 of SLD neurons, increasing SLD's downstream output[19].

REM SLEEP PRESSURE AND HOMEOSTASIS

REM homeostasis is at least partially independent from the circadian clock[21]. REM sleep pressure is mediated by a brain-derived neurotrophic factor (BDNF), accumulating after REM sleep deprivation[22]. REM sleep deprivation links with changes in the hypothalamic-pituitary-adrenal axis, metabolic balance, thermoregulation and the concentration of neurotransmitters including steroid hormones and prolactin[23].

REM SLEEP EVOLUTION AND ONTOGENESIS DURING THE LIFE-SPAN

Humans sleep less (~7 hours) than other primates, have a higher ratio of REM/ NREM sleep (~1:3.5) and a higher sleep efficiency. The luxury of excess REM sleep may be related to humans' 'earthbound' sleeping (with no risk of drop-downs due to REM-atonia)[24]. It may contribute to the maturation of networks for innovation, creativity and ideation[25]. Interestingly, REM sleep is reduced in astronauts in weightless environment, suggesting a role of gravity in REM sleep regulation[26].

REM sleep dynamics vary with aging. Neonatal sleep begins with 'active sleep' (continuous mixed fast activity with rapid eye movements and muscle twitches) the precursor of REM sleep, alternating with 'quiet sleep', the precursor of NREM sleep[27]. Its amount declines in the first months/years, when a regular alternation of NREM/REM sleep stages builds up and wakefulness last longer. During school-age, the amount of REM sleep declines further, then it remains stable in adulthood undergoing a slight reduction later[28].

The functions of REM sleep

REM sleep is believed to be strongly linked with mood regulation, creative problem solving and emotional memory consolidation[29, 30].

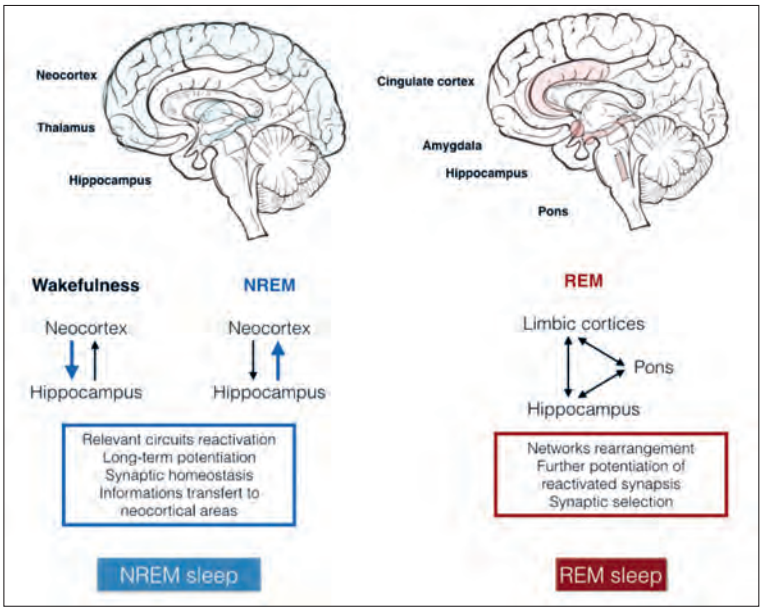

Figure 2. *Schematic representation of NREM and REM sleep dependent memory processes*

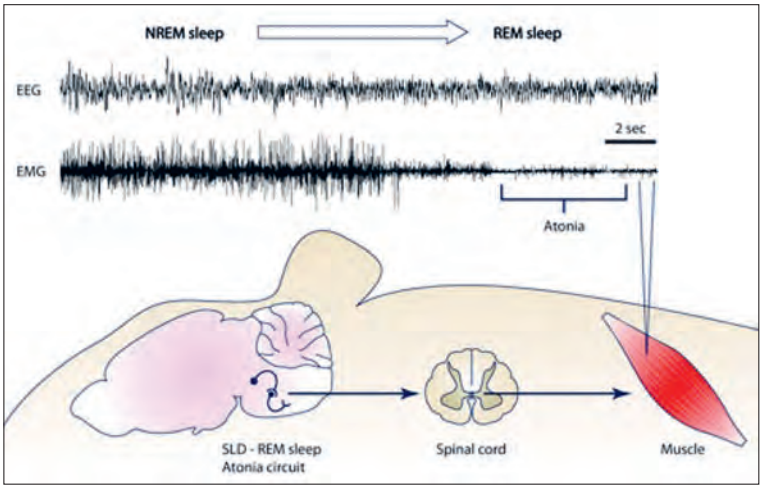

Figure 3. *The sublaterodorsal nucleus (SLD)'s central role in REM sleep atonia*[40]

While the low level of acetylcholine in NREM sleep favors the communication of the dorsolateral prefrontal cortex and the hippocampus sustaining the transfer and consolidation of declarative memory traces[31] , the high level of acetylcholine in REM sleep promotes 'emotion-driven memory-processing' involving the amygdala, the anterior cingulate and medial prefrontal cortices[32] **(Figure 2)**. The consolidation of fear memories during REM sleep possibly contributes to post-traumatic stress disorder (PTSD)[33]. REM sleep allows novel associations based on the information learned in NREM sleep[34]. Synaptic pruning and selection is likely linked to REM sleep, too[35]. Dream reports can be elicited after awakening from any sleep stages, however, REM sleep is considered the "dream-phase" with longer dreams and more bizarre contents compared to NREM sleep[36].

THE FUNCTION OF THE REM SLEEP-RELATED MUSCLE ATONIA

The function of REM sleep-related muscle atonia is mysterious. It certainly protects the sleeper from acting out dreams, and the suppression of motor activities can outweigh certain potentially sleep-disruptive stimuli. In this regard, REM-dependent muscle atonia is a sentinel of sleep resilience[37].

During RBD episodes, the rigid muscle tone of Parkinson's disease (PD) patients normalizes[38], suggesting a correcting function of REM sleep for normal waking muscle-tone. Similarly, PD's muscle rigidity parallels the lack of muscle atonia – REM sleep without atonia (RSWA) –, the basic feature of RBD, which is often a precursor and companion of PD.

THE REGULATION OF REM SLEEP ATONIA

The key members of the atonia network are the SLD and the noradrenergic precoeruleus region (PC); additionally, the caudal laterodorsal tegmental nucleus (cLTDN), the mesencephalic periaqueductal grey, orexin and melanin cells of the lateral hypothalamus, as well as nuclei of the ventromedial medulla (VmM) participate in it[39].

The glutamatergic activation of REM-on neurons in the ventral SLD[40, 41] mediates REM motor atonia through two redundant trajectories: recruiting glycinergic interneurons in the spinal ventral horn (SVH) and GABAergic/glycinergic neurons in the VmM; inhibiting SVH motor neurons in both ways.

Silencing SLD neurons suspends normal REM sleep muscle atonia resulting in RSWA, while its selective activation favors cataplexy and sleep paralysis[42–44]. A direct noradrenergic pathway links the spinal motoneurons with the locus coeruleus (LC), and a serotonergic one with the dorsal raphe (DR) both inhibiting the REM-atonia generation of the SLD[45] **(Figure 3)**.

Table 1. *REM sleep dissociation phenomena*

	Abnormally emerging/ missing element of REM sleep	State of appearance	Duration
Sleep paralysis	REM muscle atonia	Sleep-wake transition	Minutes
Cataplexy	REM muscle atonia	Wakefulness	Seconds -minute; sudden
Hypnagogic hallucination	REM sleep dreaming	Sleep-wake transition, sleep paralysis, cataplexy	Minutes?
Sleep attacks in narcolepsy or Parkinson's disease	REM sleep	Wakefulness	>Minutes
REM sleep without atonia	REM muscle atonia is absent or fragmentary	REM sleep	periods of REM sleep

Parasomnias

SEVERAL REM SLEEP PARASOMNIAS REPRESENT REM DISSOCIATION PHENOMENA

The separated ascending and descending pathways regulating the rostral and caudal components of the REM sleep pattern allow REM dissociation; i.e. REM sleep elements as dreaming or muscle atonia emerging separately in a wrong time or missing in the right time, during REM sleep **(Table 1)**. Cataplexy, sleep paralysis and hypnagogic hallucinations make positive REM sleep dissociation states (REM sleep phenomena emerge in inadequate phases), while RBD represents a negative dissociation, where the normal muscle atonia is absent or fragmentary during REM sleep **(Figure 4)**.

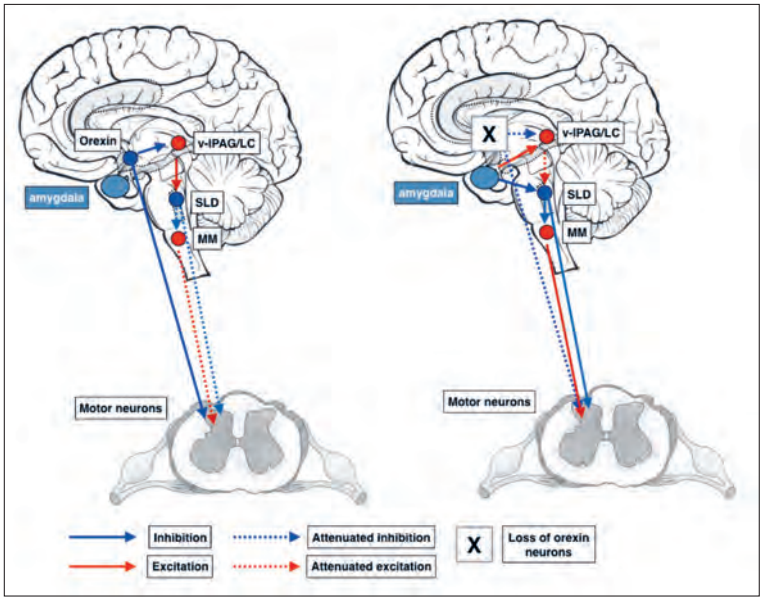

Figure 4. *Inappropriate activation of the REM sleep atonia circuitry during wakefulness is thought to produce cataplexy. Glutamatergic REM-active SLD neurons trigger the paralysis of REM sleep via stimulation of the GABAergic/glycinergic cells in the VmM. These VmM neurons send inhibitory projections to skeletal motor neurons. Under normal conditions, strong positive emotions are processed via GABAergic neurons of the CeA, which then inhibit cells in the LC and vlPAG. However, in the absence of the LH hypocretinergic neurons in cataplexy, this inhibition fails, so the REM sleep atonia circuit is released from inhibition and triggers muscle paralysis while the individual remains conscious. The inhibition of LC neurons during cataplexy removes noradrenergic inputs to motoneurons, thereby enhancing the muscle paralysis of cataplexy*

CeA: central nucleus of the amygdala, GABA: γ-aminobutyric acid, LC: locus coeruleus, LH: lateral hypothalamus, VmM: ventral medial medulla, SubC: subcoeruleus, vlPAG: ventrolateral periaqueductal gray, MN: motoneuron

SLEEP PARALYSIS WITH HALLUCINATIONS: REM SLEEP ATONIA AND DREAMING EMERGE IN WAKEFULNESS OR DROWSINESS

Sleep paralysis has been described in as early as 1664[46]. Over the centuries, it has often been attributed to the presence of evil: demons, the old hag in Shakespeare's Romeo and Juliet. In the frightening paralyzed state occurring during sleep-wake transitions (instead of REM sleep), the affected person cannot move or speak for a few minutes, experiences chest pressure, unable to call, suffocating – "something is sitting on the chest" – or feeling outside own body. It resolves spontaneously or on called by name. Sleep paralysis occurs solely or as a member of the narcoleptic tetrad. Its family accumulation suggests a genetic background[47]. Polymorphisms in the PER2 (Period Circadian Regulator 2) gene, a component

of the circadian clock mechanism, have been associated with a predisposition to sleep paralysis[48].

Multimodal hallucinations and lucid dreaming co-occur in 75% of cases[49, 50] Intruder (someone in the room) and incubus type (someone carrying out aggressive/sexual acts) hallucinations occur. Since those hallucinations are perceived as real by the individual, they may lead to even legal consequences. Due to hallucinations with "demonic significance", the condition has been sometimes linked to schizophrenia. Antidepressants (Escitalopam, Venlafaxine) have been suggested for treating the most disturbing cases, reassurance and tailored psychotherapy (meditation-relaxation therapy) may help.

REM SLEEP BEHAVIOR DISORDER: MISSING OR FRAGMENTED REM MUSCLE ATONIA ALLOWS DREAM ENACTMENT

RBD has emerged out of the big bunch of nighttime confusional states and violent behaviors, the latter reported by 1.7% of the population[51]. First described in 1986[52], RBD is a parasomnia, in that the individual "effects" his/her dreams due to RSWA, because the normal loss of muscle tone (a transient global paralysis) of REM sleep, is absent.

The International Classification of Sleep Disorders (2014) suggested the following diagnostic criteria for RBD: (1) repeated episodes of sleep-related vocalization and/or complex motor behaviors; (2) these behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep; (3) polysomnographic recording demonstrates RSWA; (4) the disturbance is not better explained by another sleep or mental disorder, medication or substance abuse[53].

RSWA is defined as sustained or intermittent elevation of chin electromyographic (EMG) tone or phasic chin or limb EMG twitching[54, 55], during at least one third of the REM sleep period. Since the persisting upper airway muscle tone may prevent some apneic episodes, RSWA can be protective against obstructive sleep apneas.

Despite the fact that RBD is a REM sleep disorder, it seems to affect sleep globally. Based on a cohort study[56], NREM micro-sleep instability reflected by the rate of CAP was lower (sleep was more stable) in idiopathic RBD patients compared to controls. The reduction of CAP rate was even more marked in the converter RBD-group (progressing to a Parkinsonian condition). Thus a lower CAP rate signalized a higher risk for conversion into a syncleinopathy.

RBD is categorized as idiopathic, or rather isolated when standing alone; and symptomatic or rather combined when associated with other disorders or states. The combined forms can be iatrogenic related to medication and other substances. They often associate to neurodegenerative diseases especially α-synucleinopathies, as well as to tauopathies, TDP-43-pathies (transactive response DNA 43 kDA binding proteinopathies), to narcolepsy and to any causes affecting the REM sleep network[57].

Prevalence

The prevalence of isolated RBD is ~ 0.38%-2% in the population >60 years-old and 5-13% in older community-dwellers doubly affecting men[58, 59]. An equal gender ratio has been reported in younger age groups[60], often in combination with narcolepsy and other conditions. There is a high rate of autoimmune comorbidity in women[61]. The disorder is tenfold more frequent in patients with mental health conditions. Additional risk factors include antidepressant use, low educational level, historic head trauma, pesticide exposure, smoking, ischemic heart disease, and inhaled corticosteroids[62].

Clinical features

RBD is characterized by sudden, vehement and fragmentary movements and speech or shouts out of sleep. There are frequent injuries caused by the patient falling out of bed or the bed partner being attacked by the half-sleeping patient enacting often horrifying dreams[61]. RBD episodes favor the second half of the night - the period of REM sleep dominance; contrasting NREM parasomnia episodes emerging in the early hours of night sleep. The patients remember their dreams often involving elements of aggression or animals[63, 64].

Melatonin 3-12 mg or clonazepam 0.5-2.0 mg usually help. Clonazepam may aggravate obstructive respiratory events and cognitive symptoms; melatonin is usually well-tolerated. Donepezil and Vortioxetine are additional treatment options. Second-line therapies include temazepam, lorazepam, zolpidem, zopiclone, pramipexole, ramelteon, agomelatine, cannabinoids, and sodium oxybate. A bed-alarm system may protect patients leaving their bed during episodes, and counselling or hypnosis might help suppressing nightmares[65, 66].

Aetiologies of RBD

Any etiology impairing the complex REM atonia network may cause RSWA/RBD. The duration

(transitory or chronic) and associated features depend on the origin of the brainstem dysfunction (drug, hypoxia in obstructive sleep apnea) or lesion (neurodegenerative, inflammatory etc.)

RBD may be an early sign of neurodegeneration offering an opportunity to understand, and - most importantly - prevent or delay subsequent neurologic impairment. In a seminal study on elderly patients with isolated RBD, 80.8% developed a parkinsonian disorder/dementia during 16 years follow up, with a mean delay of 14 years from RBD onset[67]. This high conversion-rate to neuro-degeneration was confirmed later by many additional studies.

There is a striking specificity of RBD converting to a synucleinopathy as PD, diffuse Lewy body disease (DLB), multisystem aptrophy (MS), spinocerebellar atrophy type 2, Tourette syndrome, Möbius syndrome or Smith-Magenis syndrome. The disorder also links to tauopathies and TDP 43-pathies as Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease, Guadalopean Parkinsonism and progressive supranuclear palsy[57, 58, 62, 68]. In a systematic review on 237 adult RBD patients with a non-synucleinopathy neurology conditions 19% had brain lesions, typically in the brainstem. Pontine ischemic lesions were the most frequent, but other types of structural lesions and conditions (including inflammatory, demyelinating and autoimmune, 22%) occurred too. Alzheimer's disease developed in 12% of RBD cases and other tauopathies in 9%. The high prevalence (12%) of Arnold-Chiari malformation highlighted the importance of brainstem involvement; suggesting the pathogenic role of the affected network rather than the type of lesion[69]. Based on clinical experiences, these features of RBD appearing with narcolepsy, do not progress to a neurodegenerative condition; narcolepsy seems to be protective in that respect.

Imaging features of RBD may mark the risk for Parkinson's disease

RBD-related brain changes were detected *in vivo* with structural MRI and diffusion tensor imaging (DTI): microstructural changes in the white matter of the brainstem, the right substantia nigra, the olfactory region, the left temporal lobe, the fornix, the internal capsule, the corona radiata, and the right visual stream[70]. The progression of RBD linked with parieto-occipital and orbitofrontal thinning as well as visuospatial loss, while the cognitive decline associated with parietal degeneration[71]. Isolated RBD patients' decreased striatal DAT binding[72], the loss of nigral hyperintensity on 3.0-T MRI and transcranial echo may predict short-term progress of RBD to synucleinopathy[73]. Multimodal MRI, neuro-melanin-sensitive volume-, and signal intensity measures discriminated RBD patients from controls and predict a Parkinsonian progress[74].

RBD caused by autoimmunity: anti-IgLON5 disease

Growing number of diseases have been recognized to have unexpected inflammatory or autoimmune etiologies e.g. PD[75] , Alzheimer's disease[76] and narcolepsy[77] as well as paraneoplastic limbic encephalitis and Morvan syndrome. A human leucocyte antigen (HLA) association is usually considered a hint to autoimmunity e.g. in narcolepsy, which is another REM sleep dysregulation syndrome sometimes overlapping with RBD and carrying the strongest HLA Class II association among all diseases[78]. Also RBD link with HLA class II genes: 84% of 25 RBD patients carried the DQw1 (DQB1*05,06) alleles and 28% were DR2 positive[79].

The possibility of RBD with an autoimmune background is revealed by the recognition of a novel autoimmune-neurodegenerative disease-spectrum anti-IgLON5 disease, manifesting combinations of parasomnias, obstructive sleep apnea syndrome with stridor, bulbar and limb movement disorders, axonal neuropathy and cognitive loss[80]. As an autoimmune tauopathy[81], anti-IgLON5 disease models the link between autoimmunity and neurodegeneration[82]. The hallmark of the disease is the presence of antibodies against IgLON5, a neural cell adhesion protein of unknown function. The effect of immunotherapy is not yet clear. About 80% of anti-IgLON5 patients present with sleep-related vocalizations, movements and behaviors as well as sleep-disordered breathing at age> 60, with an equal male/female ratio. Neuropathology examination shows an atypical neuronal tauopathy with neuronal loss and gliosis in the hypothalamus and brainstem tegmentum[83–85]. Video-polysomnography may reveal a NREM parasomnia with sleep-talking, simple or finalistic movements, poorly structured N2 sleep, obstructive sleep apnea with stridor and RSWA. A lymphocytic pleocytosis was found in one patient. Four syndrome combinations have been delineated: (1) insomnia, parasomnia and disordered breathing; (2) a bulbar syndrome + salivation, stridor, even acute respiratory failure; (3) a supranuclear palsy-like syndrome; and (4) cognitive decline with figural and working memory impairment, with or without chorea. Most patients carry the HLA-DRB1*10:01 and HLA-DQB1* 05:01 haplotypes (the same as isolated RBD patients) and have IgLON5 antibodies both in serum and cerebrospinal fluid. Anti-IgG1 and -IgG4 antibodies are found[86].

RBD variants and the differential diagnosis of RBD

In overlap parasomnias, status dissociatus and agrypnia excitata, fragments of partial wakefulness, NREM and REM sleep amalgamate in irregular combinations, sometimes underlined by brainstem disorders, encephalopathies, neurodegeneration or autoimmune encephalitis.

Sleep-related epileptic seizures, obstructive sleep apneas with pseudo-RBD, confusional arousals as well as nocturnal panic attacks may raise differential diagnostic issues solved by careful analysis of symptoms, clinical history video-polysomnography.

RBD and post-traumatic stress disorder

There is a peculiar link of RBD with PTSD. A motor dysfunction with increased muscle twitches during REM sleep has been early noticed in relation to stress and PTSD[87], and several case studies and war-veteran cohort studies found higher rate of RBD in PTSD patients compared even to trauma-survivors without PTSD[88]. The frequent co-occurrence of RBD and PTSD generated a distinct term - trauma-associated sleep disorder (TASD) - sharing the features of PTSD and RBD[89].

In PTSD patients, the rate of stress-related norepinephrine turn-over might have changed in the LC, leading to norepinephrine depletion and even cell death. LC's fine structural changes in relation to stress could be shown by neuroimaging in humans[90]. In rats, a single acute stressor could precipitate long-lasting changes in LC function contributing to stress-related disease[91]. Due to the persistent decrease of LC noradrenergic output to the REM atonia network, RSWA and RBD may evolve[92]. Another important mechanism potentially leading to the loss of muscle atonia in PTSD might involve stress-related changes of the Papez circuit and serotonergic pathways related to the DR nucleus[93].

RBD in PTSD might be a good example of a deep psychological impact turning to an organic condition. In addition, the specific link of RBD with PTSD justifies the diagnosis of PTSD as a distinct entity: just experiencing distress might be qualitatively different compared to experiencing distress + having PTDS (intrusion symptoms, avoidance of trauma related stimuli, mood and cognitive changes, insomnia or hypersomnia, reckless self-neglecting behavior, irritability and concentration disturbances (DSM-5)[94]. Whether RBD associated with PTSD carries the long-term risk for neurodegeneration, is unknown.

RSWA but no RBD with antidepressants?

The association of RBD/RSWA with the use of antidepressants – selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI) – has been early described[95]. A large study found an association of SSRI and SNRI use with RSWA only, curiously not accompanied by an increase of the frequency of RBD[96]. Another study found similar results: RSWA but no RBD had occurred in 8.8% of young psychiatry inpatients treated with fluoxetine, venlafaxine, mirtazapine, paroxetine, clomipramine or sertraline as well as quetiapine; thus, an association of antidepressants with a florid/hypermotor RBD has remained dubious[97]. A large study on 318 patients evidenced the association of comorbid depression and SSRI use with RBD, but a clear cause-and-effect relation between antidepressants and RBD has neither been confirmed[98].

Because antidepressants increase REM sleep muscle tone, they are routinely used in the treatment of cataplexy[99]. On the other hand, since around one third of RSWA cases of variable etiologies manifest RBD[54], the antidepressant-related increase of RSWA-rate without concomitant increase of RBD-rate needs an explanation. One may speculate that the iatrogenic increase in muscle tone is mild, sufficient just to cause RSWA, but it is insufficient to manifest RBD. Another hypothesis is that since the body-site of atonia involved by RSWA determines the clinical manifestation of RBD, RSWA affecting facial muscles only, as may be the case with antidepressants, would not lead to spectacular RBD episodes, while RSWA in limb muscles would[100].

SLEEP RELATED PAINFUL ERECTION: THE NORMAL REM-RELATED ERECTION GOES WRONG

Sleep related painful erection is a rare parasomnia, occurring in 1% of men presenting with sexual problems. It differs from the normal REM-related penile tumescence only by the associated pain awakening the individual from sleep; the patient may have normal penile erection and sexual life when awake[101]. Local origins, a vagal dysfunction and central, especially antero-lateral hypothalamic etiologies have been raised.

Baclofen has been found a good treatment option. Beta blockers, benzodiazepines and antidepressants were transitorily effective in some cases, and several additional treatments have also been used.

Summary and future challenges

REM parasomnias make an interesting and informative group of sleep disorders, rooting in the changes of the wide brainstem REM sleep network. Most of them are REM dissociation phenomena, where one or more elements of the REM sleep pattern occur in a wrong sleep state (cataplexy, sleep paralysis, hypnagogic hallucinations in wakefulness); some are absent or emerge insufficiently in their normal time (RBD). Evidencing the multilateral link with the REM atonia network, RBD, cataplexy and sleep paralysis may co-occur e.g. in narcolepsy, highlighting the dysfunctions of the atonia network with opposite-side effects.

Neurodegenerative diseases including tauopathies, TDP-43-pathies, autoimmune/inflammatory or stroke-related conditions, as well as brainstem compression syndromes as Arnold-Chiari malformation, may damage the REM atonia network. Chemical effects e.g. antidepressants or hypoxia may transitorily or permanently change the atonia network's functioning. These „functional" RBD syndromes may manifest specific symptom-localizations offering a future discrimination tool.

RBD, as an early sign of synucleinopathy (or rather a synucleinopathy itself), may carry a prognostic value, predicting or accompanying an overt neurodegenerative condition and providing opportunity of preventing or delaying it when such tools will be at hand. The special link of RBD with autoimmunity seems more than pure chance, given the important and shared HLA association of RBD and anti-IgLON5 disease, an autoimmune tauopathy. The overlap with narcolepsy, another REM sleep-related and autoimmune condition with HLA Class II association and REM sleep disturbance, needs further scrutiny.

The association of RBD with PTSD, forming together the new entity trauma-related sleep disorder, provides an example of a psychology impact turning to brain-organic. Is RBD in such cases a psychosomatic disease?

Further scrutiny of REM parasomnias may provide data for understanding the role of antidepressants in sleep regulation, the link of depressions (characterized with short REM latency) with other REM disorders, and finally, help clarifying the functions of REM sleep.

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KOGNITÍV FUNKCIÓROMLÁS VIZSGÁLATA PRAXISKÖZÖSSÉGEKBEN – TANULSÁGOK

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Hungarian https://doi.org/10.18071/isz.75.0185 www.elitmed.hu

Háttér és cél – A „Három generációval az egészségért program" praxisközösségeiben a háziorvosok feladata volt a dementia szűrése mini-COG és Mini Mental State vizsgálattal. Célul tűztük ki a bevontak szűrési eredményeinek, ezek orvos általi értékelésének és a betegek további sorsának bemutatását.
Módszerek – A bevontaknál mini-COG teszt után, dementiagyanú esetén végezték el az MMSE tesztet. A vizsgáló a kapott eredményt kóros vagy nem kóros kategóriába sorolta, rögzítette a továbbküldés megtörténtét, az adatokat egy online felületen rögzítette. Vizsgálatunk keresztmetszeti vizsgálat, a célkitűzésekben leírt paraméterek alakulását, illetve megoszlását írjuk le nyers esetszámokkal és részarányokkal. A páciensek bevonása az 55 év felettiek körében konszekutív módon történt. Csak azokat az eseteket (29 730) elemeztük, ahol rendelkezésre állt a mini-COG és az MMSE teszt eredménye, azok orvos általi értékelése, a szakellátásba való továbbküldés adatai.
Eredmények – A Mini-Cog teszt alapján a vizsgáltak 64%-ánál merült fel kognitív hanyatlás gyanúja. Misszklasszifikáció 13 015 esetben fordult elő, a Mini-Cog teszt pontszámai alapján a kognitív hanyatlás és a háziorvosok által is kórosnak gondolt elváltozás 21%-ban egyezett. Az MMSE teszt a minta 34%-ánál (10 174 fő) vetett fel dementiagyanút, a részt vevő háziorvosok 4262 (42%) főnél ítélték kórosnak az eredményt. A Mini-Cog teszt pontszámok alapján kóros értékkel rendelkező személyek 11%-a (2095 fő), az MMSE teszt pontszámok alapján dementiagyanús személyek 17%-a (1709 fő) kapott beutalót szakellátásba.
Következtetés – Vizsgálatunk a kognitív hanyatlás detektálásának gyakorlatát mérte fel az egészségügyi alapellátásban. A praxisközösségek a dementia szűrésére elfogadott eszközöket használták, a kapott eredmények értékelése és a dementiagyanús esetek szakellátásba

INVESTIGATING COGNITIVE IMPAIRMENT IN COMMUNITIES OF PRACTICE – LESSONS LEARNED

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Ideggyogy Sz 2022;75(5–6):185–190.

Background and purpose – In the "Three Generations for Health" programme, general practitioners were responsible for screening for dementia in their practices using mini-COG and Mini Mental State Examination. The aim was to present the screening results of those included, their assessment by the doctor and the further fate of the patients.
Methods – After mini-COG test, MMSE test was performed in case of suspected dementia. The examiner categorized the result as abnormal or no abnormal, recorded the referral, and recorded the data in an online interface. Our study is a cross-sectional study; the evolution and distribution of the parameters described in the objectives are described with raw case numbers and proportions. Patients aged 55 years and over were recruited consecutively. Only those cases (29 730) where mini-COG and MMSE test results were available, their assessment by the physician, and referral data to specialist care were analyzed.
Results – The Mini-COG test revealed that 64% of the subjects were suspected of cognitive decline. Misclassification occurred in 13 015 cases, with 21% of the Mini-Cog test scores matching cognitive decline and 21% of lesions considered abnormal by GPs. The MMSE test raised the suspicion of dementia in 34% of the sample (10 174 people), with 4 262 (42%) of the participating GPs considering the result abnormal. 11% (2095 people) of people with abnormal Mini-Cog test scores and 17% (1709 people) of people with suspected dementia based on MMSE test scores were referred to specialist care.
Conclusion – Our study assessed the practice of detecting cognitive decline in primary health care. The tools adopted for screening for dementia were used by practices, but the assessment of results and referral of suspected cases of dementia to specialist care were below the expected level.

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Érkezett: 2022. április 12. Elfogadva: 2022. április 26.

irányítása az elvárt szint alatt maradt. Az alapellátók dementiadetektálással, -kezeléssel kapcsolatos ismereteinek fejlesztése, illetve a szakellátással való kapcsolatának erősítése szükséges.

Kulcsszavak: *háziorvos, dementia, szűrés*

There is a need to improve primary care providers' knowledge of dementia detection and treatment and to strengthen links with specialist care.

Keywords: *general practitioner, dementia, screening*

A dementia növekvő gyakoriságú problémát jelent nagymértékű egészségügyi, szociális és gazdasági hatásokkal. A betegség világszerte egyre nagyobb terhet jelent mind az egyének, mind a társadalom számára. A Gazdasági Együttműködési és Fejlesztési Szervezet (OECD) országaiban 2017-ben a betegek száma megközelítette a 19 milliót, a róluk gondoskodó családtagok, barátok száma ennek többszöröse lehet. A társadalom öregedésével, különösen a 80 év felettiek arányának emelkedése okán, illetve hatékony terápia hiányában 2050-re a demens betegek számának 41 millióra növekedését várja az OECD[1].

A dementia magyarországi prevalenciájáról nincsenek pontos adataink, mivel nem készültek olyan hazai felmérések, amelyek célja konkrétan a dementia prevalenciájának, illetve betegségterhének felmérése lett volna[2], csak becslésekre lehet hagyatkozni, hiszen szisztematikus adatgyűjtés sem folyik. A dementia prevalenciáját világszerte vizsgáló tanulmány Európa esetében 65 éves életkor felett 6,4%-ra teszi azt, az Alzheimer típusú dementia előfordulási gyakoriságát 4,4%-nak, míg a vascularis típusút 1,6%-nak jelöli. Egy olasz vizsgálat jóval magasabb (12,4%) prevalenciaadatokat talált ugyanebben a korcsoportban[3]. A nemzetközi adatokból kiindulva Magyarországon 250-300 000 demens beteg lehet.

A fel nem ismert dementia aránya a világ legtöbb országában meghaladja a 60%-ot, a diagnózis elmaradásának ismert kockázatai a férfi nem, a 70 év feletti életkor, a háziorvos által felállított diagnózis, ugyanakkor a Mini-Mental State Exam (MMSE) használata javítja a diagnózis esélyét[4].

A háziorvosok fontos szerepet játszanak a dementia felismerésében és gondozásában. Kognitív károsodás okozta panaszokkal, tünetekkel jellemzően a családorvosi rendelőben jelentkeznek először a betegek, itt kellene megtörténnie a diagnózisgyanú felvetésének. A korai felismerés lehetővé teszi a kognitív hanyatlás módosítható okainak befolyásolását, illetve a társbetegségek – például a depresszió – kezelését[5]. A korai diagnózis lehetőséget ad a betegedukáció megkezdésére, a támogatás megszervezésére, és azzal az előnnyel is járhat, hogy a korai stádiumban kezdett terápia javíthatja a tüneteket, illetve a funkcionalitást[6]. A korai diagnózis gondoskodást nyújtók számára is időt és lehetőséget ad a „gondoskodói szerephez" való hozzászokásra, ami segíti a dementia okozta változások elfogadását, illetve a pszichés problémák előfordulási gyakoriságának csökkenésével jár. Az enyhe, illetve közepesen súlyos dementia kapcsán nyújtott kompetens gondoskodás késleltetheti az intézeti elhelyezés idejét, és javítja a gondoskodást nyújtó pszichés jóllétét[7].

A korai diagnózis mindazonáltal, ha a beteg segítség nélkül, egyedül marad, pszichés zavarokat, az önállóság, adott esetben a munka vagy jogosítvány elvesztésétől való félelmeket okozhat[8].

A „Három generációval az egészségért program" (2019–2022) elsődleges célja a szív- és érrendszeri betegségek kockázati tényezőinek és a kockázat szintjének felmérése a lakosság minél szélesebb körében a háziorvosok bevonásával, egyénre szabott beavatkozások indítása, továbbá a szívinfarktuson vagy stroke-on átesett betegek gondozása során a beteg-együttműködés javítása. A cardiovascularis fókuszon túl az érintett korcsoportokban csonttörési kockázat-, dementia- és pitvarfibrilláció-szűrés is a program része. A cél eléréséhez a program során ezen tevékenységek monitorozására, a rendszerszintű informatikai háttér megteremtésére és a Gottsegen György Országos Kardiovaszkuláris Intézet szervezésében a praxisközösségben dolgozók szakmai képzésére és folyamatos támogatására is sor került.

A programban való részvételre projektmegvalósítóként háziorvosi praxisközösségek pályázhattak. Az első körben, 2019. első félévében 453 háziorvosi és házi gyermekorvosi praxis kezdte meg szakmai programja megvalósítását 79 konzorcium keretében. Végeredményben összesen 143 konzorciumban országszerte 806 praxis vett részt a program megvalósításában.

Vizsgálati célkitűzések és módszerek

Célul tűztük ki, hogy a program során a kognitív hanyatlás szűrésébe bevont 55 év feletti populáció esetében leírást adjunk a mini-COG és az MMSE tesztekkel történt szűrések eredményeiről, illetve bemutassuk a szűrési eredmények orvos által történő értékelését és a betegek további sorsának alakulását.

A vizsgálati mintát a háziorvosi praxisközösségek által a programba bevont azon páciensek alkották, akikről az adatszolgáltatás elektronikusan megtörtént. A páciensek bevonására az 55 év feletti célcsoportból került sor a háziorvosi praxisokban, a praxisközösségi pályázatukban vállalt keretszám eléréséig. A bevonás konszekutív módon történt – a bármely okból történő rendelésen való megjelenés, illetve adminisztratív okból történő esetkezelés kapcsán – azok körében, akik a megjelölt korosztályba tartoztak, és beleegyeztek a programban való részvételbe. A praxisközösségekben a program ajánlásának megfelelően beleegyező nyilatkozat aláírását követően először mini-COG tesztet végeztek, majd dementiagyanú esetén sor került az MMSE teszt elvégzésére, ugyanakkor az orvos dönthetett úgy is, hogy negatív mini-COG esetén is elvégzi az MMSE tesztet. Kórosnak ítéltük a mini-COG-eredményt, amennyiben: 1. a szóemlékezet 1-2 pont az órateszt eredményétől függetlenül; 2. az órateszt 0 pont; 3. az órateszt negatív, de csak 2 szó ismétlése volt sikeres. A szóemlékezet és az órateszt megfelelősége esetén a kognitív károsodás gyanúját elvetettük. MMSE teszt esetén dementiagyanút a 24 pont vagy az alatti érték jelentett. A vizsgálónak a szűrés során kapott eredményt kóros vagy nem kóros kategóriába kellett sorolnia, illetve rögzítenie kellett a továbbküldés megtörténtét is.

Az adatszolgáltatást a részt vevő praxisok központilag biztosított online felületen (Icardio) végezték, ahonnan az adatokat az elemzéshez már személyazonosításra alkalmatlan módon kaptuk meg, ugyanakkor minden egyedi adatsor egy bevont pácienshez kapcsolható maradt, akinek személyazonosságát – szükség esetén – csak a saját háziorvosa tudta visszafejteni.

Vizsgálatunk keresztmetszeti vizsgálat, melynek során a vizsgálati célkitűzésekben leírt paraméterek alakulását, illetve megoszlását írjuk le. Adataink bemutatása elsődlegesen nyers esetszámokkal és részarányokkal történik. A vizsgálat 2019. január elsején indult, és a jelen elemzéshez szolgáló adatokat 2022. január 30-ig gyűjtöttük. A kiindulási mintaelemszám 89 665 volt, az adattisztítás során törlésre kerültek a duplikált rekordok, az 55 év alatti személyek; így összességében a praxisközösségekben 79 827 páciens esetében végezték el a mini-COG tesztet, az eredmény 41 582 esetben (52%) nem bizonyult kórosnak. A vizsgálat célkitűzéseinek megfelelően csak azokat az eseteket elemeztük, amelyeknél rendelkezésre állt a mini-COG és az MMSE teszt eredménye, azok orvos általi értékelése, továbbá adatok a szakellátásba való továbbküldést illetően, így a teljes körű adattisztítást követően 29 730 fő adatainak elemzésére került sor.

Eredmények

Jelen keresztmetszeti vizsgálatunkban a dementiaszűrésbe bevontak közül 10 973 (37%) férfi és 18 757 (63%) nő adatait elemeztük. Az 55–64 éves korcsoportból 9356 fő (31%), a 65–74 éves korcsoportból 11 879 fő (40%), 75 éves kor és a felett 8495 fő (29%) szerepelt a vizsgálatban.

A Mini-Cog teszten 0 pontszámot ért el 3515 fő (12%), 1 pontot ért el 5112 fő, ami a minta 17%-át jelentette. Kettő pontot ért el 4266 fő (14%) és három pontot 6255 fő (21%), ami azt jelenti, hogy a vizsgálati minta 64%-ának legalább egypontnyi vesztesége volt, azaz körükben merült fel kognitív hanyatlás gyanúja. Korcsoportos bontásban az 55–64 évesek körében a Mini-Cog teszten elért pontszámok alapján a kognitív hanyatlás gyanújának prevalenciája 56% volt (5206 fő). A 65–74 éves korcsoportban 7602 főt érintett a betegség, a korcsoportban a betegség előfordulási gyakorisága 64% volt. A 75 éves és idősebb páciensek körében négy alatti pontszámot az érintett korcsoport 75%-a (6340 fő) kapott.

Összesen 13 015 esetben fordult elő miszklasszifikáció, amelyből 12 946 (az összes eset 44%-a) esetben a háziorvos nem ítélte kórosnak azt az eredményt, ami a teszten elért pontszám alapján már dementia gyanúját mutatta, továbbá 69 esetnél volt látható, hogy kóros elváltozásként regisztrálták az amúgy normális, maximális pontszámmal rendelkező személyt (**1. táblázat**). A Mini-Cog teszt pontszámai alapján kognitív hanyatlást jelző eredmény és a háziorvosok által is kórosnak gondolt elváltozás 6202 esetben volt azonos, ami a minta 21%-át jelentette. A teszten maximális pontszámot ért el 10 513 (35%) fő úgy, hogy az eredményt a háziorvos is a normális tartományba sorolta.

Az MMSE kapcsán 19 556 fő került a normális besorolásba (a minta 66%-a). Enyhe dementia volt megfigyelhető 3260 főnél (11%), mérsékelt dementia 1056 főnél (4%). Súlyos dementia 5858 főt érintett (a vizsgált populáció 20%-a). A teszten elért pontszámok alapján 3725 férfinél és 6449 nőnél merült fel dementia gyanúja, ami mindkét esetben az adott nemen belül 34%-os prevalenciát jelentett.

1. táblázat. *A Mini-Cog teszt leíró elemzése*

		Mini-Cog 0–3		4		Összesen
		n	(%)	n	(%)	
Nem	férfi	6921	63%	4052	37%	10973
	nő	12227	65%	6530	35%	18757
Korcsoport	55–64	5206	56%	4150	44%	9356
	65–74	7602	64%	4277	36%	11879
	75–X	6340	75%	2155	25%	8495
Az orvos véleménye	kóros	6202	99%	69	1%	6271
	nem kóros	12946	55%	10513	45%	23459
Összesen		19148	64%	10582	36%	29730

2. táblázat. *Az MMSE teszt leíró elemzése*

		MMSE 0–24	25–30			Összesen
		n	(%)	n	(%)	
Nem	férfi	3725	34%	7248	66%	10973
	nő	6449	34%	12308	66%	18757
Korcsoport	55–64	2469	26%	6887	74%	9356
	65–74	3769	32%	8110	68%	11879
	75–X	3936	46%	4559	54%	8495
Az orvos véleménye	kóros	3221	76%	1041	24%	4262
	nem kóros	6953	27%	18515	73%	25468
Összesen		10174	34%	19556	66%	29730

A korcsoportos bontás szerint az 55–64 évesek körében 2469 főt érintett a betegség, ami a korcsoporton belül 26%-os előfordulási gyakoriságot jelent, a 65–74 évesek körében pedig 32%-ra emelkedett a betegséggyanú előfordulása (3769 fő). A 75 éves és a feletti korcsoportban a páciensek 46%-ánál merült fel – a teszten elért pontszámok alapján – a dementia gyanúja (3936 fő).

Összességében elmondható, hogy az MMSE teszt segítségével a minta 34%-ánál (10 174 fő) a pontszámok alapján dementia gyanúja volt felvethető. Ennek ellenére mindössze 4262 (42%) fő esetén állították a programban részt vevő háziorvosok azt, hogy a vizsgálati eredmény kórosnak tekinthető, és 58%-ban (25 468 fő) válaszolták azt, hogy nem kóros az eredmény. A teszten 24 vagy az alatti pontot elérő, kognitív hanyatlásra gyanús személyek közül 3221 fő (az összes dementiagyanúval rendelkező vizsgálatban szereplő személy 32%-a) esetében ítélték a kapott eredményt kórosnak a háziorvosok, míg a pontszám alapján dementiagyanúval rendelkező 10 174 esetből 6953 (a dementiagyanúval rendelkezők 68%-a) személyt nem kórosként jelölték meg. Nem kóros értékűnek ítélték 25 468 fő pontszámait, azonban az orvosok által 4262 gyanúsnak minősített személy közül a pontszámok alapján 1041 főnél (24%) kóros elváltozás gyanúja nem merülhetett volna fel **(2. táblázat)**.

A program során 2233 főt irányítottak a szakellátásba, ami az összes résztvevő 8%-át jelenti. Nemenkénti bontásban a férfiak 6%-át (703 főt) és a nők 8%-át (1530 főt) küldték tovább a szakellátó felé. Korcsoportok szerint az 55–64 évesek 3%-a (316 fő), a 65–74 évesek 6%-a (714 fő) és a 75 éves és a feletti személyek 14%-a (1203 fő) került továbbküldésre. A Mini-Cog teszten elért pontszámok alapján kóros értékkel rendelkező személyek 11%-a (2095 fő), a Mini-Mental teszten elért pontszámok alapján kóros értékkel rendelkező személyek 17%-a (1709 fő) kapott beutalót szakellátásba. Az eredmények háziorvosok általi értékelése alapján történt továbbküldéseket vizsgálva az látszik, hogy a háziorvosok által a Mini-Cog teszt alapján kóros tartományba sorolt 6271 fő közül 1816 főt irányítottak a szakellátás felé, ami az általuk kórosnak ítélt személyek 29%-át jelentette. Az MMSE teszt alapján összesen 4262 főnél állt fent dementia gyanúja az orvosok szerint, közülük 1921 főt küldtek a szakellátás felé, ami 45%-os arányt jelent **(3. táblázat)**.

3. táblázat. *A szakellátásba való továbbküldés nem, korcsoport, tesztek és az orvos véleménye alapján*

		Szakellátásba való továbbküldés igen		nem		Összesen
		n	(%)	n	(%)	
Nem	férfi	703	6%	10270	94%	10973
	nő	1530	8%	17227	92%	18757
Korcsoport	55–64	316	3%	9040	97%	9356
	65–74	714	6%	11165	94%	11879
	75–X	1203	14%	7292	86%	8495
Mini-Cog-pontszám	0–24	2095	11%	17053	89%	19148
	25–30	138	1%	10444	99%	10582
Mini-Cog: az orvos véleménye	kóros	1816	29%	4455	71%	6271
	nem kóros	417	2%	23042	98%	23459
MMSE-pontszám	kóros	1709	17%	8465	83%	10174
	nem kóros	524	3%	19032	97%	19556
MMSE: az orvos véleménye	kóros	1921	45%	2341	55%	4262
	nem kóros	312	1%	25156	99%	25468
Összesen		2233	8%	27497	92%	29730

Megbeszélés

A dementia számos, nagymértékű egészségügyi, szociális és gazdasági hatással járó, növekvő gyakoriságú problémát jelent a fejlett országokban, így Magyarországon is[1]. A 2019-ben publikált „Dementia in Europe Yearbook" becslése szerint 2050-ig a dementiával élők aránya – elsősorban a 70 év feletti populáció megduplázódása miatt – Magyarországon másfélszeresére nő[9].

A kognitív hanyatlás időben történő felismerése számos előnnyel jár mind a betegek, mind az őket ápolók, gondozók számára[6, 7]. A nem jól szervezett, szakmailag nem megfelelően lebonyolított és kiértékelt szűrés – elsősorban pszichés – hátrányokkal járhat[8].

Bár a kognitív hanyatlás szűrésére alkalmas eszközök rendelkezésre állnak, az érintett betegek azonosítása sokszor elmarad. Populációszintű kötelező szűrés helyett a memória- vagy egyéb kognitív zavarra panaszkodó, háziorvosi rendelőben megjelenő betegek célzott vizsgálatának gyakorlata terjedt el[10, 11], ugyanis egyelőre nem áll rendelkezésre kellő bizonyíték sem a szűrés hasznossága, sem annak esetleges hátrányai mellett. A praxisközösségekben a mini-COG és MMSE teszteket használták a dementiagyanú igazolására. Vizsgálatunkban – bár az irodalomban 65 év feletti életkorban javasolt – az 55 év feletti korosztályban történtek meg a mérések. Már az 55–60 éves korcsoportban is a vizsgált esetek negyedében felmerült a kognitív hanyatlás gyanúja, ez az arány az idősebb korcsoportokban emelkedő tendenciát mutat, rendre jelentősen meghaladva az ismert prevalenciaadatokat. Így például a 80–84 éves korosztályban az európai adatok alapján várt 15%-os prevalenciával szemben a mintánkban az esetek 50%-ában mutattak ki kóros eredményt. A jelentős különbség fakadhat abból, hogy a mintavétel a rendelőben történt, és igazodva az ajánlásokhoz, elsősorban olyan személyek bevonására került sor, akiknél tünet vagy panasz indokolta azt.

Miközben a mini-COG és az MMSE tesztek használatával nagy arányban születtek kóros eredmények, ezek adekvát interpretációja az esetek túlnyomó többségében elmaradt, sőt megfelelő értékelést követően is csupán az esetek egyharmadában került sor a szakmailag javasolt lépésre: a neurológushoz történő továbbküldésre. *Strohmaier* és munkatársai – 485 fős mintán – alapellátásban felállított dementia diagnózis esetén kevesebb mint 20%-os szakellátásba irányuló beutalási arányt találtak[12]. *Villars* és munkatársai hívják fel a figyelmet arra az alapellátásban megfigyelt jelenségre, hogy egyszerre fordul elő az alapellátásban az Alzheimer-betegség aluldiagnosztizálása és a diagnózis vagy annak gyanúja közlésének elmaradása; egyes adatok szerint a háziorvosok fele folytat ilyen gyakorlatot[5]. A diagnózis gyanújának felvetése természetesen nem könnyű, hiszen mind a betegben, mind a hozzátartozókban aggodalmakat kelt, jogi természetű kérdések, gépjárművezetői engedély visszavonásának szükségessége merülhet fel. *Bernstein* és munkatársai azt találták, hogy az alapellátó orvosok mindössze 21%-a érzi magát biztosnak abban, hogy képes a kognitív hanyatlás diagnózisának felállítására[13]. A kapott eredmények nem megfelelő értékelése az ismeretek hiányából is fakadhatott; *Heim* és

munkatársai magyarországi háziorvosok körében folytatott vizsgálatukban rámutattak arra, hogy a háziorvosok 80%-a semmilyen oktatásban nem részesült a dementia tárgykörében, és tehetetlennek érzi magát a betegek kezelését illetően[14]. Ismert a háziorvosok gyakorlatában az úgynevezett „watchful waiting" is: ahelyett, hogy időben szakellátásba irányítanák a dementiagyanús beteget, inkább csak megfigyelik egy darabig, ezzel elmulasztva a korai kezelés lehetőségét[15].

Az idősebb populáció tagjait nagyobb arányban irányították szakellátásba, ami fakadhat abból, hogy a dementiával kapcsolatos orvosi percepcióban a dementia időseket érintő betegség[16]. A referálás elmaradása ismerethiányból, szakmai bizonytalanságból, illetve nem megfelelő attitűdből, helytelen gyakorlatból fakadhat.

A dementia populációszintű szűrésének egyik ellenérve, hogy a nem kellően megalapozott diagnózisfelvetés felesleges szorongást, félelmet kelt, ebben a családorvosok gyakorlata vizsgálatunkban megfelelő volt, hiszen a negatív eredményeket jól interpretálták, és nem irányították szakellátásba ezeket a betegeket.

Következtetések

Vizsgálatunk az első olyan vizsgálat, ami széles körben mérte fel a kognitív hanyatlás detektálásának gyakorlatát az egészségügyi alapellátás területén hazánkban. A praxisközösségek a dementia szűrésére elfogadott eszközöket használták, ugyanakkor az eredmények értékelése és a dementiagyanús esetek szakellátásba irányítása az elvárt szint alatt maradt. Az alapellátók dementiadetektálással, -kezeléssel kapcsolatos ismereteinek fejlesztése, illetve a szakellátással való kapcsolatának erősítése szükséges.

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INCREASED SERUM CITRULLINATED HISTONE H3 LEVELS IN COVID-19 PATIENTS WITH ACUTE ISCHEMIC STROKE

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English https://doi.org/10.18071/isz.75.0191 www.elitmed.hu

Background and purpose – Prevalence of acute ischemic stroke (AIS) is increased in patients with coronavirus disease 2019 (COVID-19). A proposed hypothesis is increased virus-induced propensity to hypercoagulation resulting in arterial thrombosis. Our aim was to provide evidence regarding the involvement of neutrophil extracellular trap (NET) formation (NETosis) in COVID-19 related AIS.
Methods – Twenty-six consecutively enrolled COVID-19+ pneumonia patients with AIS, 32 COVID-19+ pneumonia patients without AIS and 24 AIS patients without COVID-19 infection were included to the study. Clinical characteristics of recruited patients were collected. Serum levels of citrullinated histone H3 (H3Cit; a factor of NETosis), IL-8 and C5a (mediators associated with NETosis) were measured by ELISA (enzyme-linked immunosorbent assay).
Results – H3Cit levels were significantly higher in COVID-19+ AIS patients, whereas all study groups showed comparable IL-8 and C5a levels. There were no significant differences among etiological subgroups of AIS patients with or without COVID-19. AIS patients with COVID-19 showed relatively increased white blood cell, lymphocyte, neutrophil, D-dimer, C-reactive protein and procalcitonin levels than control groups. H3Cit levels did not correlate with clinical/prognostic features and inflammation parameters. H3Cit and IL-8 levels were correlated in COVID-19 patients without stroke but not in COVID-19 positive or negative AIS patients.
Conclusion – Increased levels of inflammation parameters and H3Cit in COVID-19 related AIS suggest that

AKUT ISCHAEMIÁS STROKE-BAN SZENVEDŐ COVID-19-BETEGEK KÖRÉBEN MEGNŐ A SZÉRUM CITRULLINÁLT HISZTON H3-SZINTJE

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Ideggyogy Sz 2022;75(5–6):191–198.

Háttér és cél – A Covid-19-betegek körében megnő az akut ischaemiás stroke (AIS) prevalenciája. Egy hipotetikus mechanizmus szerint a vírus megnöveli a hiperkoagulációs hajlamot, ami arteriális thrombosist eredményez. Vizsgálatunk célja az volt, hogy bizonyítsuk: a neutrophil extracelluláris csapdaképződés (NETosis) közreműködik a Covid-19-cel összefüggő AIS kialakulásában.
Módszerek – A vizsgálatba n = 26, AIS-ban szenvedő Covid-19-pneumoniás beteget, n = 32 AIS nélküli Covid-19-pneumoniás beteget és n = 24 AIS-ban igen, de Covid-19-ben nem szenvedő beteget vontunk be. Összegyűjtöttük a betegek klinikai adatait. ELISA-val mértük a citrullinált hiszton H3 (H3Cit; a NETosis egy faktora), az IL-8 és a C5a (NETosis-asszociált faktorok) szérumszintjét.
Eredmények – A Covid-19 + AIS betegekben szignifikánsan magasabb voltak a H3Cit-szint, míg az IL-8- és C5a-szintek hasonlóak voltak valamennyi csoportban. A covidos és nem covidos AIS-betegek etiológiaalapú alcsoportjaiban nem találtunk szignifikáns különbségeket. A kontrollcsoportokkal összehasonlítva, a Covid-19 + AIS betegekben megemelkedett a fehérvérsejt-, a lymphocyta-, és a neutrophilszám, továbbá megnőttek a D-dimer-, C-reaktív protein- és prokalcitoninszintek. A H3Cit-szintek nem függtek össze sem a klinikai/prognosztikus jellemzőkkel, sem a gyulladásos paraméterekkel. A H3Cit- és az IL-8-szintek összefüggésben álltak egymással az AIS nélküli Covid-19-betegek esetében, azonban nem korreláltak a Covid-pozitív vagy -negatív AIS-betegek esetén.
Következtetés – A Covid-19-cel szövődött AIS esetében a gyulladásos paraméterek és a H3Cit megnövekedett szint-

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Érkezett: 2021. december 14. Elfogadva: 2022. február 13.

NETosis may cause susceptibility to arterial thrombosis. However, H3Cit levels do not correlate with clinical severity measures and inflammation parameters diminishing the prognostic biomarker value of NETosis factors. Moreover, the link between IL-8 and NETosis appears to be abolished in AIS.

Keywords: *COVID-19, ischemic stroke, citrullinated histone H3, NETosis, IL-8*

je azt sugallja, hogy a NETosis arteriális thrombosis iránti fogékonyságot eredményezhet. Mindazonáltal az az eredmény, miszerint a H3Cit-szintek nem korrelálnak a klinikai súlyossággal és a gyulladásos paraméterekkel, lehetetlenné teszi a NETosis-faktorok prognosztikus biomarkerként való használatát. Ráadásul úgy tűnik, hogy az IL-8 és a NETosis közötti kapcsolat megszűnik AIS esetén.

Kulcsszavak: *Covid-19, ischaemiás stroke, citrullinált hiszton H3, NETosis, IL-8*

The ongoing Coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which primarily afflicts the respiratory system. Although lung is the major target organ, almost all organ systems including the nervous system may be disturbed directly or indirectly by the SARS-CoV-2 virus[1]. Neurological symptoms appear to be triggered by a myriad of virus-induced mechanisms that are still in the process of being fully characterized. Angiotensin-converting enzyme-2 (ACE-2) receptor, one of the main targets of the virus, is present in most tissue types and is involved in the renin-angiotensin-aldosterone system, complement system, coagulation cascade and kallikrein-kinin pathway[1]. Improved understanding of the mechanisms by which SARS-CoV-2 alters the functions of these systems is required for development of novel anti-viral treatments.

Severe thrombotic events including deep vein thrombosis, pulmonary embolism, myocardial infarction and stroke may be encountered in COVID-19 patients[2]. COVID-19 has been associated with an increased incidence of ischemic stroke[3], prompting better understanding of the association between COVID-19 and stroke, which is the main contributor of neurological morbidity and mortality in this disease. Acute ischemic stroke (AIS) constitutes the majority of stroke cases in COVID-19 and increased propensity to coagulation appears to be involved in COVID-19-associated stroke[2].

Various factors have been suggested in the activation of platelets in COVID-19, such as hypoxia, vessel damage, inflammatory factors, neutrophil extracellular trap (NET) formation (NETosis) and autoimmune reactions. Histones, the most abundant proteins in the nucleus, are released into the extracellular space, where they induce platelet aggregation, neutrophil migration and endothelial cell death[4]. Platelet aggregation generally results from cross-linking of platelet integrin aIIbB3 by plasma fibrinogen. Histones bound to platelets induce calcium influx, recruit plasma adhesion proteins such as fibrinogen to induce platelet aggregation and delay fibrin digestion[4, 5]. A crucial step during NET formation is citrullination of histones by peptidylarginine deiminase 4 (PAD4). Subsequent decrease in positive charge of the histone results in a weaker binding to the DNA and chromatin decondensation. Therefore, H3Cit plays a central role in neutrophil release of decondensed and web-like nuclear chromatin. H3Cit is released into the bloodstream upon NETosis and thus serum H3Cit levels reflect the degree of NETosis[6, 7].

In severe COVID-19, neutrophils may gain a prothrombotic phenotype characterized by degranulation, increased oxidative burst and enhanced NET formation and by this directly initiate the coagulation and complement cascades in blood vessels[8]. Number of neutrophils is increased in the circulation and lungs of COVID-19 patients and neutrophil quantity correlates with the severity of the disease. Moreover, neutrophils and NETs are observed in alveoli and lung parenchyma[8]. While several mediators may trigger NETosis, IL-8 (endothelial chemokine inducing neutrophil chemotaxis) and C5a (complement cascade breakdown product with inflammatory and thrombotic action) have been found to be specifically involved in COVID-19-related NETosis[9, 10].

In this study, our main goal was to provide evidence regarding the involvement of NETosis in COVID-19 related AIS through measurement of citrullinated histone H3 (H3Cit) levels and investigation of putative correlations between H3Cit levels and clinical parameters of stroke[7]. Another target was to seek for evidence regarding the involvement of IL-8 and C5a, involved in NETosis and other inflammation mechanisms, in COVID-19-related NETosis and AIS, and look for potential correlations between these inflammation factors versus clinical features and serum H3Cit levels of COVID-19 patients.

Materials and methods

PARTICIPANT

We consecutively enrolled 26 COVID-19+ pneumonia patients admitted to our inpatient clinic within a few hours after the onset of AIS (C+S). Baseline parameters measured on admission were the National Institutes of Health Stroke Scale (NIHSS) scores and inflammation-related blood count/biochemistry parameters (white blood cells [WBC], lymphocytes, neutrophils, platelets, neutrophil/lymphocyte ratio [NLR], C-reactive protein [CRP], D-dimer, procalcitonin). Maximum modified Rankin Scale (mRS) during hospital stay, prevalence of admission to intensive care unit (ICU) and prevalence of death in the ICU were also recorded (**Table 1**). As control groups, COVID-19+ pneumonia patients without AIS (C, n=32) and AIS patients without COVID-19 infection (S, n=24) were enrolled.

AIS was diagnosed on the basis of clinical features and cranial MRI (T1-, T2-, FLAIR- and diffusion-weighted) findings. Stroke subtypes were classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[11]. During their hospital stays, all AIS patients underwent Doppler ultrasonography of the carotid arteries, electrocardiogram (ECG), transthoracic echocardiogram, 24-hour Holter monitoring, cranial and cervical computed tomography angiography (CTA) investigations on a routine basis. Patients with no pathological findings in these investigations were considered as AIS of undetermined etiology. In case of neurological deterioration, intracranial hemorrhage was ruled out by neuroimaging. None of the included patients had a history of central nervous system disorder or any other coexisting infections. Vascular risk factors were hypertension, type 2 diabetes mellitus, coronary artery disease, atrial fibrillation, hyperlipidemia and heart valve replacement. COVID-19 patients were only under antiviral treatment (favipiravir) during inclusion and patients who had received immunosuppressive medications were excluded.

COVID-19 was diagnosed with viral RNA detection using reverse transcriptase-polymerase chain reaction (RT-PCR) on nasopharyngeal swabs in all patients and found negative in control AIS patients. COVID-19 associated pneumonia was diagnosed with clinical and thorax CT findings. Days between the onset of pneumonia and AIS ranged between 0 and 8 (mean ± standard deviation; 2.5±3.0 days) in the C+S cohort. In C group, duration of pneumonia was similar during serum sampling (1-9 days; 3.7±3.1 days). All patients received a standard treatment protocol, as per national guidelines for COVID-19 and international guidelines for AIS management[12]. Ethical approval was obtained from the Institutional Review Board (Health Sciences University Clinical Research Ethics Board, no: 2779-2021) and written consent forms were obtained from the participants.

ELISA (ENZYME-LINKED IMMUNOSORBENT ASSAY)

Sera were obtained from AIS patients immediately after admission within the first few hours of stroke onset. None of the patients were under anti-coagulant, immunosuppressive or immunomodulating treatments during blood sampling. Inflammation- (listed in **Table 1**) and NETosis-associated factors were measured using the same serum samples. Serum levels of H3Cit (sensitivity=0.3 ng/ml; assay range: 0.15-10 ng/ml; Cayman Chemical, Ann Arbor, MI, USA), IL-8 (sensitivity=5.9 pg/ml; assay range: 15.6-1000 pg/ml; Cloud Clone, Katy, TX, USA) and C5a (sensitivity=27 pg/ml; assay range: 78-5000 pg/ml; Cloud Clone) were determined by ELISA kits as per manufacturer's recommendations. The results were converted to ng/ml or pg/ml under the guidance of the curves generated from the values of standards.

STATISTICS

Statistical analysis was conducted with the GraphPad Prism software (Version 5.01). Non-parametric tests were used for comparison of patient and healthy control groups due to uneven distribution of data. Thus variables were compared with Kruskal–Wallis, chi square and Mann–Whitney U tests, as required. Dunn's post-hoc test was used for post-hoc analysis in multiple-group comparisons. Correlation analysis was done with Spearman's correlation test. $p < 0.05$ was considered statistically significant.

Results

LEVELS OF NETOSIS-ASSOCIATED MEDIATORS AND CORRELATION ANALYSIS

C+S patients showed significantly higher serum levels of H3Cit than S and C patients (p=0.015). By contrast, serum levels of IL-8 (p=0.145) and C5a (p=0.376) were comparable among study groups (**Figure 1**). In both C+S and S groups, H3Cit, IL-8 and C5a levels were identical among

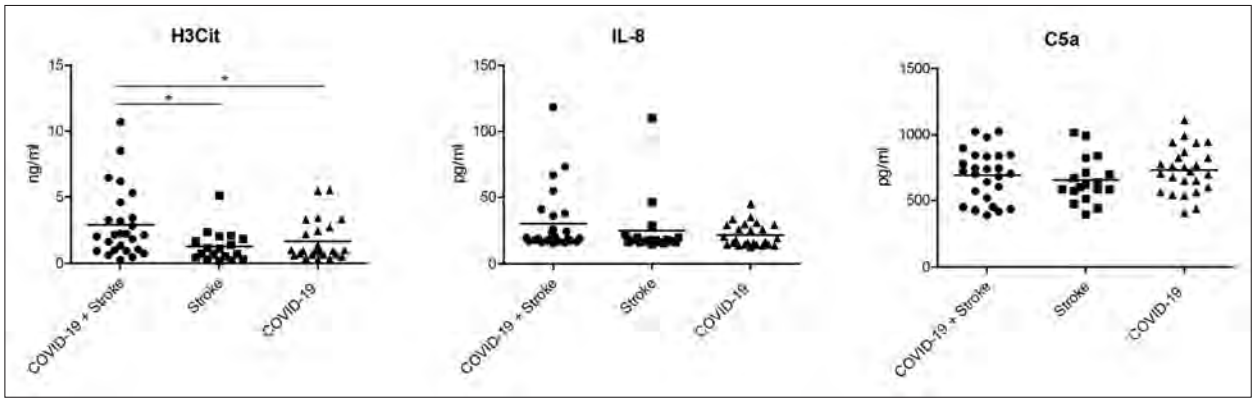

Figure 1. *Serum citrullinated histone H3 (H3Cit), IL-8 and C5a levels of patients with COVID-19 pneumonia and acute ischemic stroke (C+S), acute ischemic stroke without COVID-19 pneumonia (S) and COVID-19 pneumonia without acute ischemic stroke (C). Horizontal lines indicate mean values*

* indicates p<0.05 by Dunn's post-hoc analysis

TOAST classification subtypes (p>0.05 for all comparisons; **Figure 2**). No significant correlation was found among H3Cit, IL-8 and C5a levels versus clinical and laboratory variables (listed in **Table 1**) of C+S, C and S groups. However, H3Cit and IL-8 levels were significantly correlated in the C group. By contrast, these two variables were not significantly correlated in C+S and S groups **(Figure 3)**.

COMPARISON OF CLINICAL FEATURES AND INFLAMMATION PARAMETERS

All three study groups had comparable age, gender and vascular risk factor distribution. Likewise, C+S and S patients showed comparable distribution of stroke subtypes and large artery atherosclerosis, cardioembolism and small-vessel occlusion were the most frequently detected stroke etiologies in both

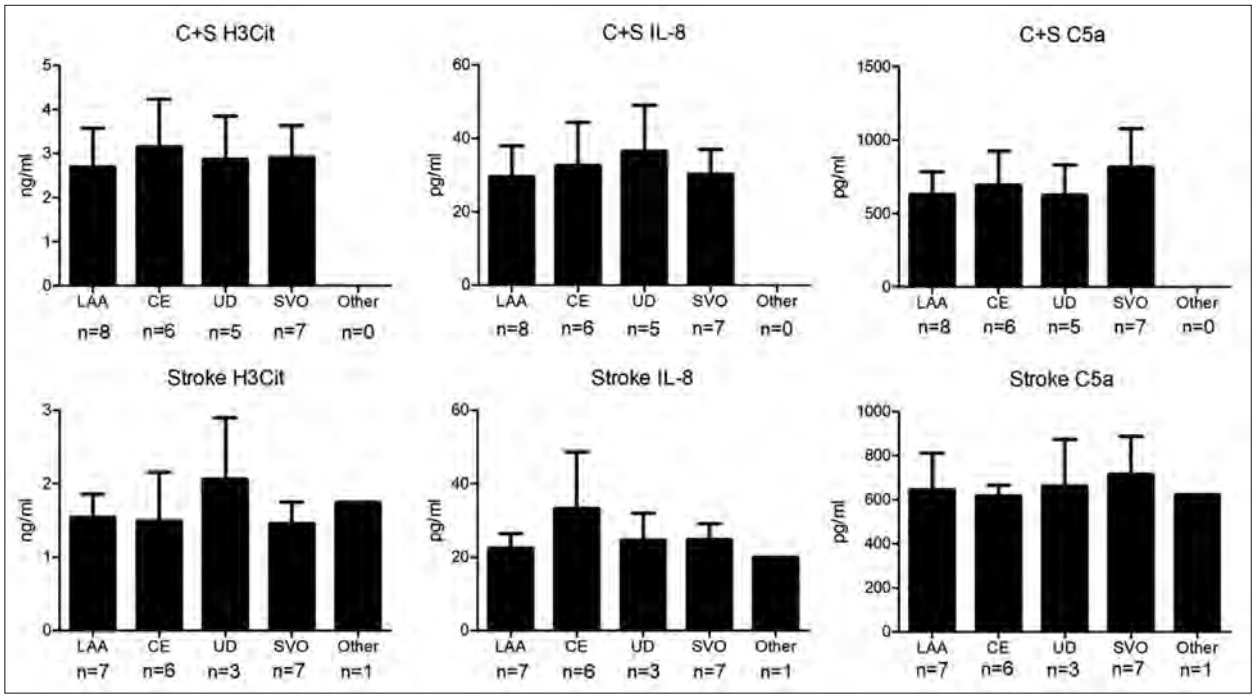

Figure 2. *Distribution of serum citrullinated histone H3 (H3Cit), IL-8 and C5a levels of patients with COVID-19 pneumonia and acute ischemic stroke (C+S) and acute ischemic stroke without COVID-19 pneumonia (stroke) among TOAST criteria subgroups (LAA, large-artery atherosclerosis; CE, cardioembolism; SVO, small-vessel occlusion; UD, undetermined etiology; other, other determined etiology). Vertical bars indicate standard errors. Number of patients for each TOAST subgroup was indicated at the bottom of the panels*

Table 1. *Comparing characteristics of patients with COVID-19 pneumonia and acute ischemic stroke (COVID-19+stroke; C+S), COVID-19 pneumonia without acute ischemic stroke (COVID-19; C) and acute ischemic stroke without COVID-19 pneumonia (Stroke; S)*

	COVID-19 + stroke (C+S) n=26	COVID-19 (C) n=32	Stroke (S) n=24	p value C+S vs C	p† for C+S vs S	p† for C vs S	p† for
Demographic data							
Age	67.5 ± 13.0	62.6 ± 17.9	63.6 ± 15.6	0.427	ns	ns	ns
Gender (men/women)	19/7	19/13	17/7	0.488	na	na	na
Medical history and acute ischemic stroke characteristics							
TOAST (n)				0.829	na	na	na
Large artery atherosclerosis	8	na	7				
Cardioembolism	6	na	6				
Small-vessel occlusion	7	na	7				
Undetermined etiology	5	na	3				
Other determined etiology	0	na	1				
Large vessel occlusion	8	na	9	0.616	na	na	na
Vascular risk factors (n)							
Hypertension	16	13	12	0.855	na	na	na
Type 2 diabetes mellitus	12	8	7				
Coronary artery disease	10	9	6				
Atrial fibrillation	6	5	7				
Hyperlipidemia	14	12	17				
Heart valve replacement	0	2	1				
ICU admission (n)	7	8	na	0.868	na	na	na
Death in ICU (n)	2	1	na	0.435	na	na	na
NIHSS	6.4 ± 4.2	na	5.8 ± 2.1	0.280	na	na	na
Maximum mRS	2.3 ± 1.7	na	2.0 ± 1.1	0.285	na	na	na
Laboratory findings							
WBC (x10^3/μl)	10.8 ± 4.9	7.5 ± 2.4	8.5 ± 2.7	*0.014*	*	*	ns
Lymphocytes (x10^3/μl)	1.7 ± 1.1	1.1 ± 0.6	1.8 ± 1.1	*0.003*	*	ns	**
Neutrophils (x10^3/μl)	8.2 ± 4.7	5.9 ± 2.5	5.8 ± 2.5	0.094	ns	ns	ns
NLR	6.8 ± 5.5	7.4 ± 5.7	4.8 ± 3.9	0.071	ns	ns	ns
Platelets (x10^3/μl)	288.2 ± 122.9	243.3 ± 91.9	257.6 ± 84.8	0.172	ns	ns	ns
D-dimer (mg/L)	1.7 ± 1.7	0.9 ± 0.6	0.9 ± 0.8	0.100	ns	ns	ns
CRP (mg/L)	97.3 ± 98.2	73.6 ± 49.9	16.2 ± 37.5	*<0.001*	ns	***	***
Procalcitonin (ng/mL)	0.3 ± 0.4	0.2 ± 0.1	0.1 ± 0.1	*0.010*	ns	**	*
Citrullinated histone H3 (ng/ml)	2.9 ± 2.6	1.7 ± 1.5	1.3 ± 1.2	*0.015*	*	*	ns
IL-8 (pg/ml)	30.4 ± 23.9	21.9 ± 8.7	25.1 ± 22.5	0.145	ns	ns	ns
C5a (pg/ml)	692 ± 192	654 ± 171	723 ± 175	0.376	ns		

TOAST, trial of ORG 10172 in acute stroke treatment classification; na, not applicable; ns, not significant; vs, versus; ICU, intensive care unit; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; WBC, white blood cells; NLR, neutrophil-lymphocyte ratio; CRP, C-reactive protein

*p<0.05; **p<0.01; ***p<0.001 by Dunn's post-hoc analysis

†Significant p values are denoted by italic characters.

groups. A single case in the S group had internal carotid artery dissection (other determined etiology). Severity of COVID-19-pneumonia was not different among C+S and C patients in terms of prevalence of ICU admission and death in the ICU. Also, C+S and S patients showed identical NIHSS and maximum mRS scores. C+S patients showed higher WBC counts than control groups. Notably, while C patients displayed lower lymphocyte counts, C+S patients had lymphocyte counts comparable to S patients. C+S patients showed trends toward displaying relatively increased neutrophil counts and D-dimer levels without reaching statistical significance. NLR values, CRP and procalcitonin levels were higher in

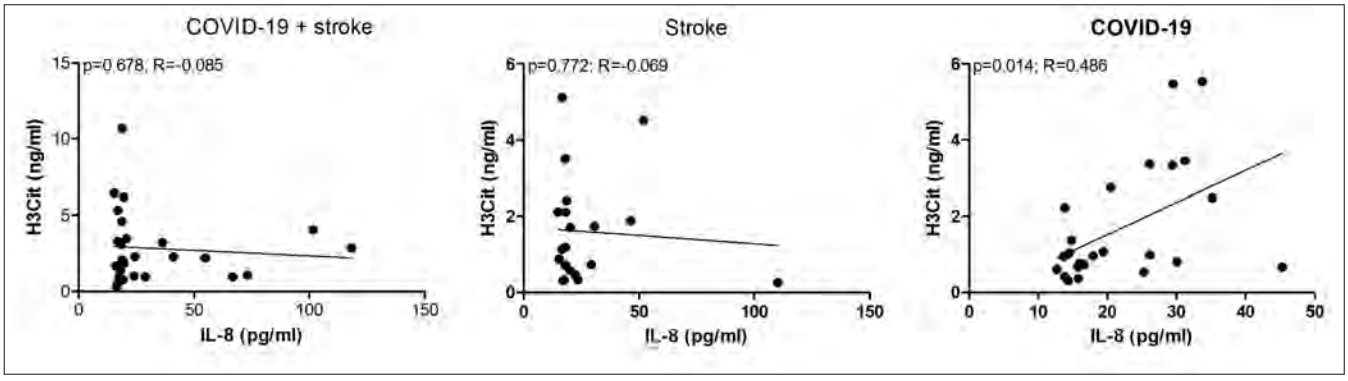

Figure 3. *Correlation between serum IL-8 and citrullinated histone H3 (H3Cit) levels in patients with COVID-19 pneumonia and acute ischemic stroke (COVID-19+stroke; C+S), acute ischemic stroke without COVID-19 pneumonia (stroke; S) and COVID-19 pneumonia without acute ischemic stroke (COVID-19; C). p and R (correlation coefficient) values denoted on the upper left corners of the quadrants were obtained by Spearman correlation test*

C+S patients than those of control groups. These differences attained statistical significance only for CRP and procalcitonin levels **(Table 1)**.

Discussion

In this study, we measured serum levels of H3Cit, a crucial element of NETosis, IL-8 and C5a in patients with COVID-19 and/or AIS, matched in terms of age, gender and disease severity and found increased levels of H3Cit in COVID-19 patients with AIS. Since H3Cit is crucially involved in NET formation[6, 7], our finding implies increased NET formation in AIS patients with COVID-19 and provides a modest support regarding the involvement of NETosis in arterial thrombosis of the brain in COVID-19 patients. Nevertheless, H3Cit levels were not correlated with measures of disease severity or levels of inflammation factors such as IL-8, C5a and procalcitonin. This finding disagrees with the potential prognostic biomarker value of NETosis factors. A likely hypothesis was that NETosis mediated immunothrombosis could be the underlying etiological factor in AIS of undetermined etiology. However, we found similar levels of H3Cit in all subgroups of TOAST classification arguing against this assertion.

NETosis is a complicated process triggered by a variety of factors. For instance, for induction of NET formation, neutrophils can release their chromatins not only by PAD4-mediated histone citrullination, but also through gasdermin-g facilitated cell membrane rupture[13]. Moreover, there are various factors of NETosis such as myeloperoxidase and neutrophil elastase, latter of which is particularly involved in anti-viral NETosis[8]. Thus, measuring levels of an extended spectrum of NETosis-related factors might result in the discovery of immunothrombosis mediators that are more closely associated with AIS occurrence and prognosis.

As a remarkable finding of our study, COVID-19+ AIS patients exhibited increased levels of inflammation-related parameters (e.g., WBC, lymphocyte, CRP, D-dimer and procalcitonin), as reported previously in other COVID-19 cohorts[14, 15]. Also, lymphopenia, which is highly prevalent in severe COVID-19[16], was not observed in AIS patients with COVID-19. Moreover, COVID-19+ AIS patients showed trends towards exhibiting increased neutrophil and NLR values, as previously reported[14]. These findings generally support the notion that neutrophil mediated inflammatory mechanisms may be involved in AIS occurring in the setting of COVID-19. However, absence of significant correlation between NETosis and inflammation parameters suggests that there is no direct causal link between these two factors and this association is probably more complex than anticipated.

IL-8 has been implicated as an important role player in pathogenesis of COVID-19 mediated tissue damage. Plasma IL-8 levels correlate with disease severity and death and inhibition of IL-8 signaling ameliorates severity of lung destruction and pulmonary microthrombosis in mice[9]. C5a, a component of the complement system, and its receptors play a critical role in the genesis of the COVID-19-associated hypercoagulable state. Disruption of C5a receptor signaling attenuates the thrombogenicity in COVID-19 and the C5-inhibiting monoclonal antibody eculizumab ameliorates findings of severe COVID-19[10, 17, 18]. Both IL-8 and C5a is known to be critically involved in NETosis[9, 10]. Thus, we looked for a possible association between these two

factors and NETosis in AIS patients. As a matter of fact, we found the previously proposed link between IL-8 and NETosis in COVID-19 patients without AIS. However, this association was abolished in AIS patients with or without COVID-19. Therefore, our results suggest that stroke might be activating alternative NETosis inducing pathways thus eliminating the regulating impact of IL-8 on NETosis induction. Overall, our results argue against involvement of IL-8 and C5a in COVID-19 associated NETosis or AIS. NETosis and subsequently increased vascular thrombosis may be caused by several different immunological factors such as IL-1 and IL-6[19, 20]. Conceivably, SARS-CoV-2 might be inducing the prothrombotic cascade directly through activation of the ACE-2 receptor without using any other inflammation mediators[21].

A drawback of our study was the low number of patients in the groups, which reduced the statistical power and the generalizability of the results. A second limitation was the low number of investigated NETosis parameters.

In brief, our results provide, for the first time, a preliminary support for the role of NETosis in COVID-19 associated ischemic stroke. Increased levels of H3Cit in COVID-19 related AIS suggest that NETosis may cause susceptibility to arterial thrombosis. However, H3Cit levels do not correlate with clinical severity measures and inflammation parameters arguing against the prognostic biomarker value of NETosis factors. Investigation of a wider panel of NETosis factors, evaluation of neutrophil activity with functional assays and histological investigation of NETosis in thrombi of COVID-19 patients in future studies may provide a more mechanistic representation of the NETosis-AIS interaction. These efforts might in due course emphasize NETosis factors as drug development targets in infection-associated AIS cases.

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COVID-19 CAN CAUSE BLINK REFLEX ABNORMALITIES

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PRINT | English | https://doi.org/10.18071/isz.75.0199 | www.elitmed.hu

Background and purpose – Neurological symptoms and complications associated with coronavirus 2019 (COVID-19) are well known. It was aimed to evaluate the brainstem and trigeminal/facial nerves and the pathways between these structures in COVID-19 using the blink reflex test.
Methods – Thirty patients with post COVID-19 (16 males, 14 females) and 30 healthy individuals (17 males, 13 females) were included in this prospective study. Individuals who previously had a positive nose swap polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 and whose previously clinical features were compatible with COVID-19 were included in the post COVID-19 patient group. Neurological examination of the participants should be normal. Blink reflex test was performed on all participants. R1, ipsilateral R2 (IR2), and contralateral R2 (CR2) waves obtained from the test were analyzed.
Results – The mean ages of healthy individuals and post COVID-19 patients were 34.0±6.4 and 38.4±10.6 years, respectively. Both age and gender were matched between the groups. R1, IR2, and CR2 latencies/amplitudes were not different between the two groups. The side-to-side R1 latency difference was 0.5±0.3 and 1.0±0.8 ms in healthy individuals and post COVID-19 patients, respectively (p=0.011). One healthy individual and 12 patients with post COVID-19 had at least one abnormal blink reflex parameter (p=0.001).
Conclusion – This study showed that COVID-19 may cause subclinical abnormalities in the blink reflex, which includes the trigeminal nerve, the seventh nerve, the brainstem, and pathways between these structures.

Keywords: *blink reflex, brainstem, COVID-19, facial nerve, trigeminal nerve*

A COVID-19 A PISLOGÁSI REFLEX RENDELLENESSÉGÉT OKOZHATJA

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Ideggyogy Sz 2022;75(5–6):199–205.

Háttér és cél – Jól ismertek a koronavírus 2019 (Covid-19) fertőzéshez társuló neurológiai tünetek és szövődmények. Vizsgálatunk célja az volt, hogy a pislogási reflex tesztjével értékeljük az agytörzsi és a trigeminus/facialis idegek és az ezek közötti idegpályák működését Covid-19 betegség esetén.
Módszerek – Prospektív vizsgálatunkba 30 poszt-covidos beteget (16 férfi, 14 nő) és harminc egészséges kontrollszemélyt (17 férfi, 13 nő) vontunk be. A poszt-covidos betegcsoportba olyan személyeket vontunk be, akik orrgarati kenetmintája polimeráz láncreakcióval pozitívnak bizonyult súlyos akut respiratorikus koronavírus 2019 szindrómára, és akik korábbi klinikai tünetei megfeleltek a Covid-19 betegség diagnózisának. A beválasztáshoz a résztvevők neurológiai vizsgálata normáleredményt kellett adjon. A pislogási reflex tesztjét valamennyi résztvevőn elvégeztük. Elemeztük a pislogási reflex R1, ipsilateralis R2 (IR2) és contralateralis R2 (CR2) hullámait.
Eredmények – Az átlagos életkor az egészséges kontrollcsoportban és a poszt-covidos betegcsoportban 34,0 ± 6,4 és 38,4 ± 10,6 volt. A két csoport megegyezett életkorban és a nemek arányában is. Az R1, IR2 és CR2 latenciák/amplitúdók nem különböztek a két csoport között. Az oldalak közötti R1-látenciakülönbség 0,5 ± 0,3 és 1,0 ± 0,8 volt az egészséges kontrollcsoportban és a poszt-covidos betegcsoportban (p = 0,011). Egy egészséges kontrollszemélynek és 12 poszt-covidos betegnek volt legalább egy abnormális pislogásireflex-paramétere (p = 0,001).
Következtetés – Tanulmányunk kimutatta, hogy a Covid-19 az agytörzset és a trigeminus/facialis idegeket, valamint az ezek közötti idegpályákat is tartalmazó pislogási reflexkör szubklinikus rendellenességét válthatja ki.

Kulcsszavak: *pislogási reflex, agytörzs, Covid-19, facialis ideg, trigeminusideg*

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Érkezett: 2021. október 31. Elfogadva: 2022. február 6.

Since the last months of 2019, the viral infection (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected almost the whole world. COVID-19 does not only affect the respiratorium, but also causes problems in many systems, including the nervous system. The number of studies showing that COVID-19 can cause abnormalities in the central or peripheral nervous system is increasing[1-5]. Neurological symptoms may be the first sign or may occur during the disease. It is well known that neurological complaints such as loss of taste (ageusia) and loss of smell (anosmia) may occur[5, 6]. Brainstem or cranial nerve involvement may be one of the neurological complications of COVID-19[4, 7, 8]. The blink reflex test can evaluate nerve conduction in pathways between trigeminal/facial nerves and the brainstem regions associated with these nerves[9, 10]. In this study, we aimed to investigate the effect of COVID-19 on these cranial nerves and brainstem by using blink reflex test.

Methods

STUDY DESIGN AND SUBJECTS

This study was conducted prospectively in the Clinical Neurophysiology Laboratory of Adana City Training and Research Hospital between September 2020 and August 2021. Thirty post COVID-19 patients and 30 healthy individuals were included in the study. Individuals with the following findings were considered to be post COVID-19 patients: 1) A positive nose swap polymerase chain reaction (PCR) test for COVID-19 at least 4 weeks ago and a negative PCR test for COVID-19 between 10 and 14 days after this positive test; 2) Fever and/or persistent cough and/or dyspnea and/or severe widespread body pain during acute infection; 3) Complete recovery or drastic reduction of the symptoms mentioned in the second item within four weeks after the positive PCR test. Electrodiagnostic tests of post COVID-19 patients were performed at least four weeks after the PCR test was positive. Participants were excluded from the study if they had one of the following conditions: 1) Disease that may cause polyneuropathy such as diabetes mellitus; 2) Findings consistent with polyneuropathy and/or neurodegenerative disease, and/or cranial neuropathy found by previous nerve conduction studies or neurologic examination; 3) History of cerebrovascular disease or demyelinating disease, or cranial neuropathy. Clinical features of COVID-19 patients and data from blink reflex and nerve conduction studies of all participants were analyzed. Ethics committee approval was given by Adana City Training and Research Hospital Ethics Committee (number: 60/958). Written consent was obtained from all participants.

NERVE CONDUCTION STUDIES AND BLINK REFLEX

Nerve conduction studies and blink reflex were performed with Cadwell Sierra Summit EMG unit (Cadwell Laboratories, Kennewick, Washington, USA). Superficial electrodes were used for recording and stimulation. High and low filters for motor and sensory nerve conduction studies were set to 20Hz-2kHz and 20Hz-10kHz, respectively. Stimulation was applied supramaximally. The sweep speed for the motor and sensory nerve conduction tests were 5 ms/division and 1 ms/division. The sensitivity for motor and sensory nerve conduction studies was set to 2 mV/division and 10 μV/division, respectively. Nerve conduction study was performed if the extremity temperature was above 32 degrees. Cold extremities were heated. Nerve conduction tests were performed on the right or left upper and lower extremities of the patients. For median, ulnar, posterior tibial, and perineal motor nerve stimulation, the distance between the stimulation point and the recording electrode placed on the wrist/ankle was 5 cm, 5 cm, 10 cm, and 8 cm, respectively. Sensory nerve conduction velocity was calculated using peak latency. The amplitude of both compound nerve action potential (CNAP) and compound muscle action potential (CMAP) was calculated by measuring peak to peak. F-wave studies were performed with 10 supramaximal stimulations and the latency of the earliest occurring F-wave was analyzed.

Blink reflex was performed by applying the methods suggested in previous studies[9, 10]. The low and high filters for the blink reflex were 10 Hz and 10 kHz, respectively. Blink reflex test was performed bilaterally. Sweep speed and sensitivity were 5-10 ms and 100-200 μV, respectively. The stimulation point was the supraorbital foramen and the intensity of the stimulation was 10-15 mA. The stimulation duration was set to 0.1 ms. At least four stimulations were performed for each eye. The eyes of the patients were open during stimulation. Four surface electrodes were used for recording. The distance between the active and reference electrodes was 2 cm, and the electrodes were placed in the orbicularis oris muscle in the lower part of the eye. The latency of the earliest potential was recorded. Among the potentials obtained with the blink reflex, the amplitude of the highest potential in the peak-to-peak measurement was analyzed. The latency of the

Table 1. *Comparison of nerve conduction test findings between healthy individuals and post COVID-19 patients*

Nerve conduction study parameters	Healthy Individuals (n=30) (mean±SD)	Post COVID-19 Patients (n=30) (mean±SD)	P value*
Median nerve			
CMAP amplitude (mV)	17.5±5.0	16.0±5.8	0.284
CMAP distal latency (ms)	3.0±0.4	2.9±0.4	0.392
Motor NCV wrist-elbow segment (m/s)	62.1±5.6	60.0±4.5	0.173
F-wave latency (ms)	26.2±1.7	26.4±2.4	0.762
CNAP amplitude (μV)	14.9±4.4	16.9±5.5	0.156
Sensory NCV 2nd finger-wrist segment (m/s)	47.4±5.7	47.9±5.7	0.709
Ulnar nerve			
CMAP amplitude (mV)	15.2±3.3	15.3±3.1	0.688
CMAP distal latency (ms)	2.3±0.3	2.3±0.3	0.604
Motor NCV wrist-below elbow segment (m/s)	63.2±4.7	64.0±5.3	0.366
Motor NCV below elbow-above elbow segment (m/s)	57.5±6.3	55.8±7.6	0.354
F-wave latency (ms)	26.8±2.1	26.4±2.3	0.333
CNAP amplitude (μV)	13.4±3.6	14.4±5.2	0.633
Sensory NCV 5th finger-wrist segment (m/s)	46.3±4.1	47.3±6.1	0.766
Posterior tibial nerve			
CMAP amplitude (mV)	12.9±5.5	12.5±5.0	0.918
CMAP distal latency (ms)	3.7±0.7	3.9±0.6	0.437
Motor NCV ankle-popliteal fossa segment (m/s)	48.0±6.2	49.4±6.2	0.306
F-wave latency (ms)	46.8±3.7	46.6±3.3	0.470
Sural nerve			
CNAP amplitude (μV)	19.2±5.2	17.5±9.3	0.074
Sensory NCV (m/s)	46.0±6.7	45.5±7.2	0.651

*: Mann-Whitney U test. CMAP: compound muscle action potential; CNAP: compound nerve action potential; n: number; NCV: nerve conduction velocity; SD: standard deviation

earliest potential was recorded. The amplitudes of the potentials were measured from peak to peak. Among the potentials obtained with the blink reflex, the amplitude of the potential with the highest amplitude was recorded. The amplitudes and latencies of ipsilateral R1 (R1), R2 (IR2), and contralateral R2 (CR2) were included in the analyses. The blink reflex was considered abnormal if at least one of the following was abnormal: 1) Absence of R1 / IR2 / CR2 potentials; 2) R1 latency > 13 ms; 3) IR2 latency > 41 ms; 4) CR2 latency > 44 ms; 5) Side-R1 latency to-side difference > 1.2 ms; 6) Side-to-side difference of R2 latency > 8 ms[10].

STATISTICAL ANALYSIS

Categorical variables were expressed as frequency and percentage. For numerical data, mean ± standard deviation and minimum-maximum were used. Pearson Chi-square and Fisher's exact tests were used for the analysis of categorical variables. Group comparisons were made with the Mann-Whitney U test. It was considered statistically significant when the P value was <0.05. The Statistical Package for the Social Sciences (SPSS IBM Corp; Armonk, NY, USA) 22.0 was used for statistical analysis.

Results

Thirty healthy individuals (17 male, 13 female) and thirty post COVID-19 patients (16 male, 14 female) were included in the study. The mean ages of healthy individuals and post COVID-19 patients were 34.0±6.4 (range 21-44) and 38.4±10.6 (range 20-59) years, respectively. Age and gender were not different between the two groups (p=0.190, p=0.795). Participants were not vaccinated for COVID-19. During acute infection, 11 patients had fever, 14 coughed, 11 had widespread pain, 3 had dyspnea, 8 had loss of smell (anosmia), 4 had loss of taste (ageusia), 9 had headache. There were four patients whose thorax computed tomography findings were compatible with COVID-19 pneumonia. Low molecular weight heparin and favipiravir were given to all patients. None of the patients were admitted to the intensive care unit or hospital service.

The mean of the interval between the time the PCR test for COVID-19 was positive and the time the electrodiagnostic tests were administered to the patients was 80.8±64.6 (range 28-240) days. **Table 1** shows the comparison of the findings of the nerve conduction study between the two groups. The comparison of parameters from the blink reflex

Table 2. *Comparison of blink reflex test findings between healthy individuals and post COVID-19 patients*

Blink reflex test parameters	Healthy Individuals (mean±SD)	Post COVID-19 Patients (mean±SD)	P value*
Right			
R1 latency (ms)	10.1±0.9 (n=30)	10.4±1.1 (n=30)	0.290
IR2 latency (ms)	29.5±3.6 (n=30)	30.9±3.3 (n=30)	0.085
CR2 latency (ms)	30.7±4.1 (n=30)	32.3±5.0 (n=29)	0.228
R1 amplitude (μV)	358.0±233.2 (n=30)	448.0±199.3 (n=30)	0.060
IR2 amplitude (μV)	305.7±184.2 (n=30)	326.0±193.6 (n=30)	0.599
CR2 amplitude (μV)	229.3±129.0 (n=30)	274.8±116.7 (n=29)	0.098
Left			
R1 latency (ms)	10.1±0.8 (n=30)	10.2±1.0 (n=30)	0.615
IR2 latency (ms)	29.7±3.2 (n=30)	31.2±3.9 (n=27)	0.139
CR2 latency (ms)	31.0±4.0 (n=29)	31.9±4.0 (n=26)	0.553
R1 amplitude (μV)	433.3±292.8 (n=30)	457.0±238.5 (n=30)	0.407
IR2 amplitude (μV)	304.7±184.4 (n=30)	310.0±144.9 (n=27)	0.554
CR2 amplitude (μV)	231.7±167.9 (n=29)	267.7±162.5 (n=26)	0.323
Side-to-side latency difference			
R1 (ms)	0.5±0.3 (n=30)	1.0±0.8 (n=30)	0.011
IR2 (ms)	1.9±2.1 (n=30)	2.4±1.9 (n=27)	0.137
CR2 (ms)	2.2±1.6 (n=29)	2.8±2.3 (n=25)	0.426

*: Mann-Whitney U test was used. CR2: contralateral R2; IR2: ipsilateral R2

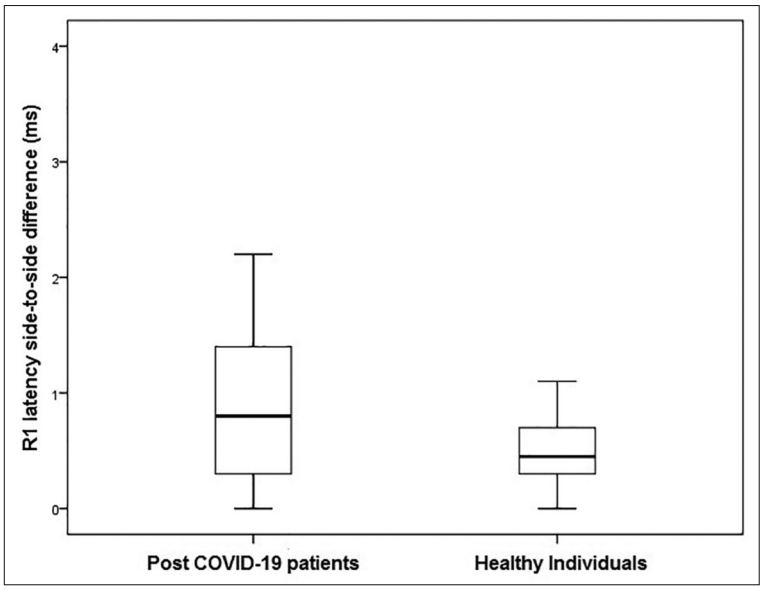

Figure 1. *Comparison of side-to-side R1 latency differences between healthy individuals and post COVID-19 patients*

tests between healthy individuals and patients with post COVID-19 is shown in **Table 2**. **Figure 1** shows the comparison of side-to-side R1 latency differences between groups. Both R1 and right IR2 potentials were obtained in all participants. Right CR2 potentials in one, left CR2 in four, and left IR2 potentials in three of the post COVID-19 patients could not be obtained. One healthy individual had no left CR2 potential. **Figure 2** shows the blink reflex study of a post COVID-19 patient whose left CR2 potential could not be obtained. The latencies of the potentials obtained from the blink reflex tests of healthy individuals were normal. The side-to-side R1 latency difference was >13 ms in 9 of 30 post COVID-19 patients. One of the 29 post COVID patients had delayed right CR2 latency. **Table 3** shows the comparison of blink reflex abnormalities between groups. The clinical and electrodiagnostic features of patients with blink reflex abnormalities are shown in **Table 4**.

Discussion

It is thought that COVID-19 may cause neurological complications in both the central and the peripheral nervous systems[1-6]. In this study, there were findings suggesting that there may be blink reflex abnormalities in post COVID-19 patients. The R1 potential obtained from the blink reflex test reflects the physiology of the trigeminal nerve and its main sensory nucleus in the pons, the facial nucleus in the pons and facial nerve, the pathways between these structures. R2 potentials are associated with the trigeminal nerve, spinal trigeminal nucleus in the medulla oblongata

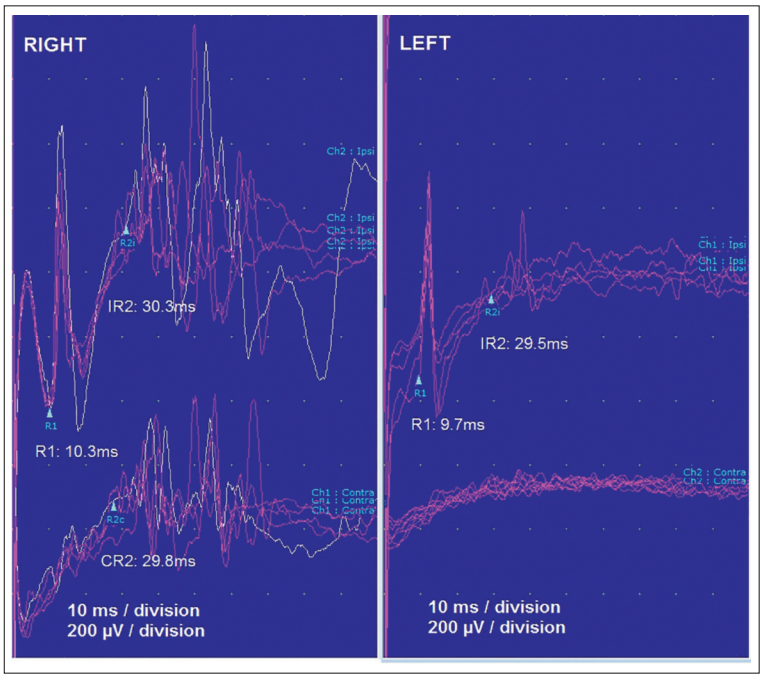

Figure 2. *Blink reflex test of a post COVID-19 patient. [Patient 26 (Male, 20 years old). Left CR2 could not be obtained. In addition, the side-to-side R1 latency difference was 1.6 ms]*

and pons, facial nucleus, facial nerve, and connections between these structures[10].

Abnormalities in R1 and R2 potentials were found in post COVID-19 patients in this study. Therefore, our findings suggest that patients with post COVID-19 may have abnormalities in the trigeminal/facial nerves, brainstem regions including the pons or medulla oblongata, or in the pathways of blink reflex. However, due to the lack of somatosensory evoked potential studies and imaging methods, it is not known exactly which region or regions are involved. The pathophysiology of neurological complications has not been clearly elucidated. The blink reflex abnormality found in this study can be explained by olfactory spreading route. Anosmia is well known in COVID-19[5, 6]. It has been reported that other coronoviruses can enter the nerve from the olfactory nerve endings and spread from there to the brain regions, including the brainstem[11]. SARS-CoV-2 may follow a similar pathway and affect the brainstem. It is known that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors, and transmembrane protease serine 2 (TMPRSS2) is important for SARS-CoV-2. The fact that some researchers argue that ACE2 and TMPRSS2 may be present in the olfactory nerve may explain the spread of SARS-CoV-2 to the brainstem or other brain regions via the olfactory nerve[12]. However, there is an article suggesting that ACE2 and TMPRSS2 are found in epithelial sustentacular cells rather than in the olfactory nerve[13].

It has been reported that there may be brainstem involvement in COVID-19[7, 14]. In one of these reports, blink reflex tests were performed in eleven COVID-19 patients admitted to the intensive care unit[7]. In that report, in line with the results of our study, abnormalities were found in R2 potentials. However, while that study was about severe COVID-19 patients admitted to the intensive care unit, none of the patients in our study were hospitalized in the intensive care unit or hospital service. Neurological examinations of the patients were also normal. This suggests that COVID-19 may subclinically affect the blink reflex. Also in our study, abnormalities in R1 potentials were also found. Side-to-side R1 latency difference was also higher in COVID-19 patients than in healthy individuals. These findings may indicate that not only the brainstem but all components of the blink reflex, includ-

Table 3. *Comparison of blink reflex abnormalities between groups*

Blink reflex parameter	Number of Healthy Individuals		Number of post COVID-19 Patients		P value*
	Normal	Abnormal	Normal	Abnormal	
Right R1 latency	30	0	24	6	*0.024*
Right IR2 latency	30	0	30	0	-
Right CR2 latency	30	0	28	2	0.492
Left R1 latency	30	0	27	3	0.237
Left IR2 latency	30	0	27	3	0.237
Left CR2 latency	29	1	26	4	0.353
At least one abnormality in blink reflex parameter	29	1	12	18	*0.001*

*: Fisher's exact test was used. CR2: contralateral R2; IR2: ipsilateral R2

Table 4. *Clinical and electrodiagnostic features with blink reflex abnormalities*

Patient No	Age (years)	Gender	Time of the Edx tests* (days)	Loss of smell	Loss of taste	Dyspnea	Thorax CT abnormality	Blink reflex abnormality
2	38	M	30	-	-	-	-	Left R1
5	37	F	31	-	-	-	-	Right R1
7	39	M	73	-	-	-	-	Right R1
11	31	F	30	+	+	-	-	Right CR2
14	47	M	118	+	+	-	-	Right R1, Left IR2
15	56	F	63	+	-	+	+	Left R1
16	28	M	122	+	-	-	-	Left R1
20	41	F	98	-	-	-	-	Right R1
21	37	M	30	-	-	-	-	Right CR2, Left IR2, Left CR2
22	30	F	28	+	-	-	-	Left IR2, Left CR2
25	24	M	39	-	-	-	-	Right R1, Left CR2
26	20	M	31	-	-	-	-	Right R1, Left CR2

*: Time interval between the time of positive PCR test for COVID-19 and the time of Edx tests. CT: computed tomography; CR2: contralateral R2; Edx: electrodiagnostic; F: female; IR2: ipsilateral R2; M: male

ing the trigeminal and facial nerves may be affected in COVID-19. Cranial neuropathies associated with COVID-19 have been reported[4, 8, 15]. However, the findings from routine nerve conduction tests are not different between post COVID-19 and healthy individuals, which may indicate that blink reflex abnormality may be associated with brainstem abnormality rather than cranial neuropathy.

Post-infectious neurological complications such as acute disseminated encephalomyelitis and Guillain-Barré syndrome have been reported[16, 17]. In addition, Miller-Fisher syndrome associated with COVID-19, which is one of the variants of Guillain-Barré syndrome, has also been reported[18, 19]. Cranial nerve involvement is known in Guillain-Barré syndrome or its variants, and the mechanism of blink reflex abnormality found in this study may be explained by the pathophysiology of these diseases. These diseases are known to occur as a result of immune-mediated mechanisms. It can be thought that these neurological complications and our findings develop by immune-mediated mechanisms rather than the direct effect of the virus.

There were some limitations in this study. First, the interval between the onset of complaints and the time of electrodiagnostic tests was variable. This may have affected the outcome of the electrodiagnostic tests. But this interval was at least twenty-eight days in all patients. We think that further studies including blink reflex test to be performed on COVID-19 patients during acute infection will be useful to understand the pathophysiology of neurological complications in COVID-19. Second, as we mentioned before, the patients did not have imaging tests of the brain/brainstem, and somatosensory evoked potential studies were not performed on patients. Therefore, it cannot be known whether the origin of the blink reflex abnormality is the brainstem or the cranial nerves. However, it should be kept in mind that the neurological examinations of the participants were performed in detail and individuals with abnormalities in the neurological examination were not included in the study. Nerve conduction tests were performed on two extremities instead of three in order to exclude polyneuropathy in the participants, which may be one of the limitations. Finally, the possibility that some healthy individuals may have asymptomatic COVID-19 infections may be a limitation. However, it should be noted that blink reflex abnormalities in COVID-19 patients were also determined as previously suggested[9, 10], not only according to the blink reflex parameters obtained from healthy individuals.

In conclusion, this study showed that blink reflex abnormalities may occur in COVID-19. There may be subclinical involvement of the nerve conduction between the fifth/seventh cranial nerve and the brainstem regions associated with these nerves in COVID-19 patients.

All authors contributed equally to every part of the article.

FUNDING
This study did not receive any funding.
DISCLOSURE OF INTEREST
The authors have no conflicts of interest to declare.

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COVID-19 AND POST-POLIOMYELITIS SYNDROME: COINCIDENCE?

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English https://doi.org/10.18071/isz.75.0207 www.elitmed.hu

Although severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel virus, many central and peripheral nervous system manifestations associated with coronavirus disease-19 (COVID-19) infection have been reported. Beyond the neurologic manifestations, we may still have much to learn about the neuropathologic mechanism of SARS-CoV-2 infection. Here we report a case of post-poliomyelitis syndrome (PPS) related to COVID-19 and attempt to predict the possible pathophysiologic mechanism behind this association.

Keywords: *COVID-19, post-poliomyelitis syndrome, immune system, pathophysiology*

COVID-19 ÉS POST-POLIO SZINDRÓMA: VÉLETLEN EGYBEESÉS?

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Ideggyogy Sz 2022;75(5–6):207–210.

Bár a súlyos heveny légúti szindrómát okozó koronavírus-2 (SARS-CoV-2) új vírus, az általa okozott koronavírus-19 betegség (Covid-19) már eddig is számos esetben járt együtt központi és perifériás idegrendszeri manifesztációval. A neurológiai manifesztációkon túl még a SARS-CoV-2-fertőzés neuropatológiai mechanizmusairól is sokat kell tanulnunk. Esetismertetésünkben bemutatjuk egy Covid-19-cel összekapcsolható post-polio szindróma kialakulását, és kísérletet teszünk az összefüggés hátterében feltételezhető patofiziológiás mechanizmus előrejelzésére.

Kulcsszavak: *COVID-19, post-polio szindróma, immunrendszer, patofiziológia*

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Érkezett: 2022. január 4. Elfogadva: 2022. április 18.

In 2019, coronavirus disease-19 (COVID-19) was first identified in Wuhan, China, and was recognized as a global pandemic by the World Health Organization (WHO) in 2020. Since then, many manifestations of central and peripheral nervous system involvement related to COVID-19 have been reported. Although there are no data showing motor neurons infected by coronaviruses, about 1% of coronavirus infections result in motor neuron infection, which may cause some motor dysfunction and paralysis[1]. In this report, we describe post-poliomyelitis syndrome (PPS) in an infected patient with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), for the first time.

Case report

A 45-year-old male with childhood-onset poliomyelitis was admitted to our hospital with progressive weakness, numbness and fatigability in his right lower limb lasting for 15 days. He tested posi-

Table 1. *EMG-findings of the patient at admission*

Muscle	Spontaneous act. Fib	PSW	Voluntary act. Amp	Dur	Poly	IP
Left gastroc caput med	0/10	0/10				0 act
Left tibialis anterior	0/10	0/10				0 act
Left rectus femoris	0/10	0/10				0 act
Left biceps	0/10	0/10	+	+	+	-
Left abd. pol. brevis	0/10	0/10	+	+	+	-
Left abd. digiti minimi	0/10	0/10	+	+	+	-
Left ext. dig. communis	0/10	0/10	+	+	+	-
Right biceps	0/10	0/10	+	+	+	-
Right gastroc caput med	3/10	4/10	+	+		-
Right rectus femoris	3/10	4/10	+	+		-
Right tibialis anterior	3/10	4/10	+	+		-
Right abd. pol. brevis	0/10	0/10	+	+	+	-
Right abd. digiti minimi	0/10	0/10	+	+	+	-
Right ext. dig. communis	0/10	0/10	+	+	+	-

tive for SARS-CoV-2 via an oropharyngeal swab and was quarantined for 10 days before admission. He did not see any physicians during these 10 days. In his medical history, after poliomyelitis, he developed weakness and atrophy of bilateral lower and upper limb muscles, more prominently in the lower extremities. Before COVID-19, he was able to walk on crutches, but later he used a wheelchair. When we retrospectively reviewed his medical records, it revealed that he had mild weakness in both upper limb muscles with the strength of -5/5, also paraparesis with 4/5 in the right lower limb and 1/5 in the left lower limb proximally and distally before Covid-19. In his neurologic examination, cranial nerves were intact. He had mild weakness in both upper limb muscles with the strength of -5/5, also paraparesis with 3/5 in the right lower limb and 1/5 in the left lower limb proximally and distally. Deep tendon reflexes were absent in the lower limbs and depressed in the upper limbs. The rest of the neurologic and systemic examination was normal. His laboratory tests showed a high level of hemoglobin A_{1c} and he was diagnosed as having diabetes mellitus by the endocrinology department. Other blood test results were normal including serum creatine kinase levels. Contrast-enhanced cranial magnetic resonance imaging (MRI) was normal. Cervical, thoracic, and lumbar spinal MRIs were done and lumbar MRI showed scoliosis. Nerve conduction studies (NCS) and electromyography (EMG) were performed. The motor NCS of the right peroneal and tibial nerves revealed low amplitude compound muscle action potential. Motor NCS of the left peroneal and tibial nerves were unobtainable. Motor NCS of the upper limbs and all sensory NCS were normal. In the EMG study, there were features of chronic denervations in muscles of both bilateral upper limb and the right lower limb, and there was no voluntary activity in the left lower limb. EMG also revealed signs of active denervations in right lower limb muscles **(Table 1)**. We offered to perform a lumbar puncture, but he didn't accept. We also excluded other conditions with EMG and imaging. At the 6th month follow-up examination, he had ongoing weakness with the strength of -3/5 in the right lower limb proximally and distally. His control EMG was the same as the previous. According to the clinical results and EMG findings, the patient was diagnosed as having PPS and was referred to physiotherapy.

Discussion

PPS refers to a clinical syndrome of new-onset muscle weakness, pain, and fatigue that may occur several decades after healing from acute poliomyelitis. Acute poliomyelitis results in lower motor neuron degeneration, and after the acute phase, reinnervation via distal axonal sprouting occurs in denervated muscle fibers. This compensatory mechanism continues as a denervation/reinnervation process until deterioration happens because of the overactivity of the surviving motor neurons. Aging, immune dysregulation, increased metabolic demand, premature dropout of muscle fibers and motor units, and the persistence of poliovirus are considered to be the decompensatory causes in the pathophysiology of PPS[2].

One hypothesis for the pathophysiology of PPS

is that the persistence of genetic viral materials has the potential to upregulate the transcription of cytokine genes and induce the production of cytokines, as a result dysregulating the inflammatory and immune system response. Inflammatory mediators such as interleukin- (IL) 2, IL-4, IL-10, interferon- (IFN) γ, and tumor necrosis factor- (TNF) α were detected in the cerebrospinal fluid (CSF) of patients with PPS. Also, inflammatory changes in the spinal cord and skeletal muscle biopsies have been reported in the literature. It is suggested that these cytokines may cause a smouldering inflammatory response and a sustained, inert neuronal dysfunction that can compromise the function or viability of already stressed and overactivated surviving motor neurons[3, 4].

COVID-19 can be a fatal syndrome characterized by severe acute respiratory syndrome caused by SARS-CoV-2. SARS-CoV-2 has 79.5% and 50% genetic resemblance to other coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively. SARS-CoV-2 and other coronaviruses exhibit neurotropic characteristics. COVID-19 causes both peripheral and central nervous system involvement[5, 6].

Coronavirus infection leads to neuronal degeneration via several possible mechanisms such as direct infection, angiotensin-converting enzyme 2- (ACE 2) or immune-mediated, and hypoxia. Neuronal death by direct infection occurs in viral infections via several mechanisms such as cell lysis, oxidative stress, and mitochondrial dysfunction. Although there are no data showing motor neurons infected by coronaviruses, about 1% of coronavirus infections result in motor neuron infection causing some motor dysfunction and paralysis[7].

SARS-CoV-2 induces neuroinflammation and oxidative stress. Cytokine storm, caused by the overproduction of inflammatory factors after coronaviruses, induces neurodegeneration and neuronal dysfunction and is reported as the leading cause of death in patients with COVID-19. In addition, an important proinflammatory mediator, IL-6, which is elevated in COVID-19, can cause an immune response in the nervous system[8, 9].

The European Federation of Neurological Societies (EFNS) task force recommended the use of diagnostic criteria of PPS based on Halstead's definition from 1991 with emphasis on the new muscle weakness. Thereafter, the EFNS task force suggested that the criteria published by the March of Dimes in 2000 should be considered as universal criteria for PPS. In accordance with these criteria, the essential clinical feature for the diagnosis of PPS is new muscle weakness or muscle fatigability that should be persistent for at least 1 year. Although no objective test is available that can reliably and specifically diagnose PPS, needle EMG is helpful to document the evidence of motor neuron involvement or to determine or exclude other neurologic disorders that might mimic the new symptoms of PPS[10].

In the differential diagnosis of PPS, Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis (AFP) in the post-poliomyelitis eradication era. After the initial progressive phase, patients with GBS reach a plateau phase that can last from days to weeks. 60–80% of patients with GBS are able to walk independently 6 months after disease onset, with or without treatment[11].

In this context our case has some limitations of the diagnosis of PPS. Although the patient has weakness for 6 months to date and on his control examination he had ongoing weakness and fatigue, this time duration is not enough to confirm the diagnosis as PPS. Even though a lumbar puncture could not be done as the patient didn't accept, Guillain-Barre syndrome was excluded in the differential diagnosis, because he had ongoing weakness and muscle fatigability for 6 months. After excluding GBS in the differential diagnosis, even if the 1-year period has not expired, the patient was diagnosed with PPS because of his progressive worsening for 6 months and his EMG being compatible with PPS.

To the best of our knowledge, this is the first case report of PPS related to COVID-19. A case report of a 23-year-old female patient with COVID-19 described steroid-responsive diffuse anterior horn cell disease[12]. Taking into account these two patients and the relation of PPS and COVID-19 with the inflammatory system, we thought that para-infectious dysregulation of the immune system caused by COVID-19 might trigger the decompensatory basis of PPS.

Conclusion

Regarding the antecedently reported neurologic manifestations of COVID-19, this is the first case of SARS-CoV-2 associated with PPS. The underlying mechanism of lower motor neuron degeneration related to COVID-19 is presumably the immunologic dysregulation. However, further studies with pathophysiologic data are necessary to support a causal relationship.

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TIKTOK AND TICS: THE POSSIBLE ROLE OF SOCIAL MEDIA IN THE EXACERBATION OF TICS DURING THE COVID LOCKDOWN

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English https://doi.org/10.18071/isz.75.0211 www.elitmed.hu

Background and purpose – Over the past year, many cases with newly onset or significantly exacerbated tic disorders were observed worldwide, where some aspects of the clinical presentation or the symptomatology were atypical for established tic diagnoses. Our purpose was to describe the atypical cases and raise relevant diagnostic issues.
Methods – Consecutive cases with atypical tic presentations were documented.
Results – Five atypical tic cases are described. These cases shared some common characteristics, most notably the fact that all of them had been exposed to online presentation of ticking behaviour on social media platforms prior to the de novo development or exacerbation of their tics.
Discussion – Even though the order of events suggests causality and therefore the diagnosis of a functional tic disorder, unambiguous criteria for classifying atypical tics as functional symptoms are lacking. Differentiating neurodevelopmental and functional tics in childhood is currently problematic.
Conclusion – Based on the currently unresolved issues in differential diagnosis, the importance of watchful waiting and behavioural interventions is highlighted to avoid unwarranted pharmacotherapy.

Keywords: *tic, Tourette, social media, functional neurological symptom disorder, conversion disorder*

TIKTOK ÉS TICEK: A KÖZÖSSÉGI MÉDIA LEHETSÉGES SZEREPE A TICEK EXACERBÁCIÓJÁBAN A COVID-JÁRVÁNY ALATT

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Ideggyogy Sz 2022;75(5–6):211–216.

Háttér és cél – Az elmúlt év során világszerte többször jelentek meg újonnan kialakult vagy jelentősen súlyosbodott tictüneteket mutató esetek, amelyeknél a klinikai kép vagy a tünetek bizonyos aspektusai nem feleltek meg a ticzavarok hivatalos kritériumainak. Célunk a saját gyakorlatunkban előforduló atípusos esetek leírása és a felmerülő diagnosztikai problémák felvetése.
Módszerek – Az egymás után megjelenő atípusos ticeseteket dokumentáltuk.
Eredmények – Öt atípusos ticesettel találkoztunk. Az esetek néhány közös jellegzetességgel rendelkeztek, kiemelten azzal, hogy az anamnézisben a ticek de novo kialakulását vagy exacerbációját megelőzően a betegek tictüneteket néztek közösségi médiafelületeken.
Megbeszélés – Habár az események sorrendje oksági kapcsolatra, ebből következően funkcionális ticzavar diagnózisára utal, a funkcionális tünet diagnózisához nem állnak rendelkezésre egyértelműen alkalmazható kritériumok. A neurodevelopmentális és funkcionális ticek elkülönítése gyermekkorban sok problémát vet fel.
Következtetés – A differenciáldiagnosztikai hiányosságok miatt a beavatkozás nélküli betegkövetés és viselkedésterápiás eszközök alkalmazása javasolt a szükségtelen gyógyszeres kezelés elkerülése érdekében.

Kulcsszavak: *tic, Tourette, közösségi média, funkcionális neurológiai tünet zavar, konverziós zavar*

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Érkezett: 2021. november 25. Elfogadva: 2022. január 4.

Tics are repetitive, stereotypical, excessive movements or vocalizations. They are perceived as involuntary, although a certain degree of suppressibility sets tics apart from other disorders characterized by extra movements, like myoclonus or chorea. Further blurring the line between involuntary and volitional phenomena is the possible appearance of so-called functional (or psychogenic; in this paper we will refer to them as functional) tics, which are thought to have a different aetiology from tic disorders[1]. Certain characteristics that diverge from the typical course and presentation of tic disorders point to a possible functional aetiology. The frequency of atypical, possibly functional tics appears to have increased during the COVID-19 pandemic in 2020 and 2021[2, 3]. In this period, especially during and after the 3rd wave of the COVID-19 pandemic in Hungary, we saw several patients with atypical tics, some of whose clinical features suggested a functional aetiology. In this paper, we present five consecutive, possibly functional, tic cases where social media plays a potential role in the development and exacerbation of these symptoms.

Case descriptions

CASE 1

The 16-year-old girl was referred to our hospital for involuntary motor and vocal symptoms. History: Her family history was negative for tic disorders and other psychiatric disorders. Her medical history includes dizziness at age 14; assessments did not reveal any organic causes and the symptom resolved spontaneously.

Symptoms at admission: When admitted to our neurology ward in January, 2021, she reported that she had been experiencing involuntary symptoms since August, 2020: head rolls, repetition of words, eye rolling, and hand jerks; with an abrupt worsening in her symptoms at a New Year's Eve party. Afterwards, she had attacks of these symptoms lasting for 20 to 25 minutes. She recorded one of these attacks on video to be shared on TikTok later; the video showed continuous motor and vocal symptoms while she was talking about her experiences, but the symptoms stopped when she was reaching for the phone to turn off the recording. She did not report any premonitory urges. Her symptoms largely resolved within a day after the admission, and were barely observed or reported during her inpatient stay. EEG, cranial MRI, and serum autoimmune panel exams showed no abnormalities.

A child psychiatric consultation with a tic specialist took place on February 16, about 6 weeks after the abrupt worsening of her symptoms. She and her mother did not report any symptoms since her discharge from the hospital (January 24, 2021) (Yale Global Tic Severity Scale/YGTSS Total Tic Score was 0). On inquiry, it was revealed that for months before her first symptoms appeared, she had been following the daily life of a young person with Tourette's syndrome on the TikTok video sharing platform.

Medical opinion: Although the cross-sectional appearance of the symptoms corresponded to tics, the sudden appearance and remission of the symptoms, the unusual age of onset, her gender, the way voluntary actions appeared to temporarily suspend the symptoms, and the readiness to publicly display her symptoms were not typical for tic disorder categories.

She was followed up in March, and it was reported that her symptoms had never returned.

CASE 2

The 10-year-old female patient was referred to our hospital's emergency unit for sudden-onset motor symptoms.

History: In 2019, at age 9, she was hospitalized for a sudden-onset tic-like vocalization (throat clearing), which spontaneously remitted within a month. Immediate family members were infected by COVID-19 virus in March, the patient did not have any symptoms and was not tested for the infection. Family history was negative for neurological and psychiatric disorders, including epilepsy, tics, attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).

Symptoms at admission: In April, 2021 she was hospitalized for sudden-onset involuntary motor symptoms (shoulder, leg, and whole-body jerks) which first appeared about 2 weeks before, at bedtime. After a few days, the frequency of these symptoms significantly increased and was present all day. The patient's YGTSS Total Tic Score was 9 at admission. The patient reported that symptoms decreased when performing a voluntary action, like eating. She was not able to voluntarily suppress the symptoms and did not report any premonitory sensations or urges. Her neurological exam was negative. EEG showed normal background activity with no epileptiform signs. Her blood test and COVID-19 serology test results were negative.

Medical opinion: Based on the atypical appearance of the initial symptoms (only at bedtime), the atypical age at the first symptoms (9 years old), the

female gender, the relatively abrupt onset, the distractibility, the lack of premonitory sensations and the inability to suppress the tics, functional etiology was suggested. A potential factor in the possible functional symptom generation was that she was a passionate online follower of *Billie Eilish*, a pop star immensely popular among pre-teen and teenage children, who is open about her Tourette's disorder.

Follow-up information was not available, as the patient could not be reached at the contact details provided by the family.

CASE 3

The 14.5-year-old girl was referred to our clinic for newly onset motor and vocal symptoms.

History: Her family history was negative for neurological or psychiatric disorders. Her medical history was uneventful.

Symptoms at admission: Her first motor symptom (head jerk) appeared in January 2020, and continued to reappear about once a month. In April, 2021, the number and frequency of symptoms increased: symptoms were present almost continuously, and neck stretches, head jerks, squeaks, sniffles, whistles, mouth clicks and smacks, occasional rhythmic shaking of the legs emerged. She could suppress the symptoms for short periods. Since the motor symptoms made her nauseous, the patient avoided eating and lost 4 kg. Her symptoms interfered with speaking and writing. She also reported a constant tension-type headache since the beginning of April. She was admitted to the neurological ward on April 19, 2021. The Total Tic Severity Score of the YGTSS was 27. When asked about social media use, the patient reported that she had contacted and was following a girl with Tourette's syndrome on TikTok. Her neurological status was negative. Cranial MRI showed no abnormalities. EEG during wakefulness showed normal activity. Laboratory results showed a mildly elevated antistreptolysin titer, but the throat swab culture was negative. Although the current symptoms had not been preceded by any signs indicative of an infection, due to the antistreptolysin titer elevation, a course of penicillin was administered, but her symptoms remained unchanged. A psychiatric consultation was requested and haloperidol was recommended.

Medical opinion: Based on the unusual age of onset, her gender, the potential online influence and the complete lack of effectiveness of medication, the possibility of a functional aetiology was suggested.

Follow-up: After a month, the pharmacotherapy did not reduce the symptoms and it was discontinued. As her symptoms were largely unchanged, behavioural treatment was recommended.

CASE 4

The 12-year-old girl was hospitalized with increasingly intensive numbness, dizziness and tremor, which changed to tics during her inpatient stay.

History: Her family history includes transient tic-like symptoms in several male relatives. The family history is otherwise negative for neurological and psychiatric disorders. Her medical history was uneventful.

Symptoms at admission: On April 12, 2021, the patient developed dizziness, numbness in the left forearm, and tremor in the head and neck muscles. The intensity and duration of her symptoms increased, so she was hospitalized. Physical and neurological examination did not find anything abnormal. Laboratory tests and blood pressure values were normal, ophthalmological and ear-nose-throat examinations did not reveal any abnormalities. Her EEG was normal. Psychological examination described anxiety and lower-than-average mood.

On the 3rd day of her hospitalization, her symptoms changed: eye blinking, tongue clicking, head and neck jerks, and shoulder shrugs appeared, and the dizziness, numbness and tremor disappeared. Tiapride was started and the patient was discharged with diagnoses of anxiety disorder and transient tic disorder. It is important to note that her roommate at the hospital displayed similar symptoms (also reported here, see Case 3), they soon became friends and watched TikTok videos of people with tics together.

A child psychiatric consultation took place approximately one and a half months later (June, 2021). The YGTSS Total Tic Score was 19 at the time. The parent and child reported that her tic-like symptoms significantly improved the day after discharge but had not improved any further, even though the dose of the medication had since been increased. The patient did not report any specific premonitory urges, and she was unable to suppress the symptoms. After in-person education was reinitiated in May, she felt disturbed by other students noticing her symptoms, and her parents decided to keep her home-schooled until the end of the school year.

Medical opinion: Although the cross-sectional appearance of the symptoms and the positive family history suggested a tic disorder, the age at the

first symptoms, the abrupt symptom onset, the female gender, the vague neurological symptoms preceding the tic-like phenomena, the concurrent psychological symptoms, her roommate's very similar symptoms, questionable or no response to medication, the inability to suppress the symptoms, the lack of premonitory urges, and the benefit associated with symptoms (exemption from school attendance) were in favour of a functional aetiology. Therefore, a gradual withdrawal of the drug and behavioural therapy were recommended.

Follow-up: For 2 months, her symptoms remained unchanged, then, as abruptly as they appeared, they resolved and had not returned until the finalization of the manuscript.

CASE 5

The 15-year-old female patient was referred to our clinic for involuntary motor symptoms.

History: No information was available about the family history, as the patient was adopted. Her medical history included hand and arm tremors at age 4; no neurological abnormalities were found and no treatment was recommended; the tremor gradually disappeared. She had repeatedly developed low-grade temperature increases since kindergarten, the cause could never be established. During the 2020 spring lockdown, the patient's mood worsened, and she received a few months of psychotherapy.

Symptoms at admission: She was hospitalized in April for the reappearance of her hand and arm tremors, and along with them, the emergence of involuntary movements (head and shoulder jerks) accompanied by varying vocalizations (sometimes simple noises, sometimes words). Physical and neurological exams, an EEG and laboratory exams were performed, none of them revealed anything abnormal, so she was discharged and psychiatric consultation was recommended.

The child psychiatric consultation took place in June. YGTSS Total Tic Score was 11 at the time. By June, the tremor had completely disappeared and her tic-like symptoms had largely ameliorated. When asked about potential social media influences, the patient stated she loved Billie Eilish and had actively researched online for the symptoms of Tourette's.

Medical opinion: Based on her age at symptom onset, her gender, the atypical presentation (same movements accompanied by varying vocalizations), the presence of other functional motor symptoms and the potential social influence, an atypical tic disorder was diagnosed and a functional aetiology was suggested.

Follow-up: A month after the consultation, none of the symptoms were present.

Discussion

In the first half of 2021, we saw several patients with involuntary motor and vocal symptoms that did not fit into the usual presentation or course of a tic disorder and shared some common characteristics. They were all female, their symptoms were accompanied by vague somatic or neurological complaints, their symptoms had an abrupt start or exacerbation, and none of the patients reported premonitory urges associated with the symptoms. None of them were able to suppress the symptoms and medication, if tried, was ineffective. The symptoms of all patients reached a severity warranting hospitalization during the lockdown. Finally, all patients had observed ticking behaviour online or in person before their first symptoms appeared.

Although individual cases can differ significantly from each other, tic disorders show remarkable similarity all over the world[4]. Certain characteristics, like an atypical course, the lack of premonitory urges, the inability to suppress tics, female gender, the presence of other functional motor symptoms, the lack of efficacy of usually effective medications, the lack of tics in the family history, the absence of the usual rostrocaudal symptom distribution, interference with voluntary actions, absence or atypical appearance of pali-, echo-, and coprophenomena, and the lack of the typical waxing and waning of the symptoms may indicate psychological, rather than neurodevelopmental reasons[1, 5]. Also, functional (ie. not neurodevelopmental) tics often have an abrupt onset or are triggered by a specific event, which is not usual for tics; patients with tics tend to try to camouflage their symptoms, whereas patients with functional tics usually do not[6]. It has also been suggested that if neurological symptoms are alleviated by psychological methods, it means they are functional[7].

It is important to recognize, however, that the previously listed characteristics are based on statistical probability, so certain atypical features in an individual patient do not prove that the symptoms are functional. For example, symptom onset does usually occur before or around the beginning of school, with 93% of patients displaying their first symptoms by age 10; however, about 6% of patients develop their first tics between ages 10 and

15, and a further 1% will experience tic onset after 15 years of age[8]. Males are usually more likely to develop tics than females, but the female-to-male ratio varies significantly (from 1:10 to 1:3) in different studies[8], and for transient tics lasting no more than 1 or 2 months, the female-to-male ratio was as low as 1:1.6[9]. Similarly, it is well known that medications do not work for all patients with a tic disorder, or that many patients, especially children, do not experience premonitory urges[10]. As for using the effectiveness of psychological treatment to classify tics as functional, the most recent guideline of the American Academy of Neurology (AAN)[11] found higher confidence in the evidence for the efficacy of behavioural treatment in tic reduction than for the efficacy of any medication. The fact that exposure to tics presented on social media platforms, especially TikTok, before symptom exacerbation is frequently featured in the history of atypical cases all over the world has lead several authors to suggest a relationship[2, 3]. However, suggestibility has long been known as a core trait of tics[12], such a fundamental one that an expert guideline, based on a systematic review, uses it as a criterion to classify medically unexplained chronic cough as a tic cough (and not a habit or psychogenic cough)[13]. A recently published study about group behavioural interventions for tics noted that some (primarily vocal) tics actually worsened during the treatment period, a phenomenon attributed to the high reactiveness of some tics to socially mediated reinforcers[14]. The way social media may affect tics has not been systematically studied yet, but it is likely that even though the interaction occurs through a screen, suggestibility and socially mediated reinforcement work just the same. In fact, it has been demonstrated that tics increase when patients watch a video recording of tics[15].

Currently, no single criterion used for making the distinction between functional tic-like movements and tics can unequivocally set the two groups apart[1]. Usually, the final decision is based on the sum of all symptoms, however, the number of present or missing clinical features required to make a final decision has not been established, and it is not known if any of these features carry more weight than others[1]. Features nudging the clinician towards the suspicion of a functional tic disorder are often not explicitly incompatible with a neurodevelopmental diagnosis, only represent a significantly less likely, but still established subpopulation of patients.

Conclusion

An unambiguous distinction between tics and their functional counterparts in children is currently impossible. However, it seems that the presentation of tics by social media influencers, especially during a period of scarcity of the normal in-person social stimuli, may lead to the development or exacerbation of tics (or tic-like movements) in children watching these videos. A systematic look into the matter clarifying whether this relationship actually exists and if so, what mechanisms play a role, is necessary. Until then, paediatric experts working in neurology or mental health services should place special emphasis on the collection of accurate and detailed information about the tics or tic-like symptoms of their patients, and, in accordance with the 2019 AAN guideline[11], watchful waiting and behavioural interventions should precede pharmacological treatment.

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