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ORIGINAL PAPER

Andressa Bonito Lopes (ABCDFGH), Dhebora Espindola Amboni (ABCDFGH), Marilis Macedo Schmidel (ABCDFGH), Miriélly Junges Maciel (ABCDFGH), Alberito Rodrigo de Carvalho (ACDFGH), Gladson Ricardo Flor Bertolini (ACDEFGH)

Evaluation of the dose-response for electrostimulation with Aussie current in the core strength

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ABSTRACT

Introduction. Muscle strengthening to improve joint stability is widely used in the rehabilitation process, and the use of neuromuscular electrical stimulation is a useful tool, but the use of Aussie current still has little documentation about its effectiveness.

Aim. To verify if there is a dose-response effect to Aussie current, both in the strength and in the static and dynamic stability of the deep pelvic lumbar muscles.

Material and methods. 39 volunteers divided into four groups, one control and three electrostimulation with intensity variation, one with intensity at the contraction threshold (GT), another with intensity maintained at 20% more (G20), and another with intensity maintained at 30% more (G30) than the intensity at the contraction threshold. The intervention lasted four weeks, with three weekly sessions lasting 15 minutes. Initially and after the intervention period, the strength and stability of the deep muscles of the pelvic lumbar region were measured in a static and dynamic manner by a biofeedback pressure unit.

Results. There was a significant increase of pressure under the lordoses in the pre- and post-evaluation moments, there were no differences in the evaluation of indirect force (dynamic stability), but there was an increase in the time for GT. The effect sizes presented advantages for the electrostimulated groups in static stability.

Conclusion. The doses used did not promote significant statistical differences, but the effects were positive for the electrostimulated groups, especially with respect to static stability.

Keywords. muscle strength, paraspinal muscles, spine, stabilization, transcutaneous electric nerve stimulation

Introduction

The lumbar region is part of the lumbar-pelvic complex described as "core", and in this region most body movements are initiated. In view of this, the stabilization of this region is of great importance to promote a more effective transmission of force, distributing the loads generated equally to all joints, which prevent the overload of some structure of this complex.[1-4]

The muscles that promote the stabilization of the lumbar spine are the multifidus and abdominal trans-

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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verse, the multifidus present a predominance of type I fibers, with an important mechanical role in force transfer due to the important control of lumbar lordosis.[5,6] Thus, in order to have a previous recruitment of these muscle groups, providing static and dynamic control to the spine, central stabilization training is recommended, with techniques like core stability exercises, Isostretching, Global Postural Reeducation, and Pilates, to ensure functional stability and reduce the incidence of injuries and discomfort in the pelvic lumbar region.[1,7-10]

One of the therapeutic possibilities for strengthening important core muscles is neuromuscular electrical stimulation (NMES), which is widely used in rehabilitation, and has shown positive results for underutilized muscle groups, with joint stabilization, increased strength, tone and muscle trophism.[11-16] Among the forms the Aussie Current is considered comfortable and effective, with a medium frequency base current characteristic, modulated at low frequency.[17]

There are several studies that address joint strengthening and stabilization with the use of NMES, but the literature is still poor in relation to the use of the Aussie current in lumbar-pelvic stabilization, especially with variation in stimulation doses, since dose-response studies are more common with respect to low frequency stimulation.[11,12,15,16,18-21] Therefore, the present study aimed to verify if there is a dose-response effect for Aussie current electrostimulation applied to the low back muscles, both in the strength and in the static and dynamic stability of the deep lumbar-pelvic musculature.

Aim

To verify if there is a dose-response effect to Aussie current, both in the strength and in the static and dynamic stability of the deep pelvic lumbar muscles.

Material and methods

This is a quantitative, experimental, randomized study carried out at the Physical Rehabilitation Center of the Universidade Estadual do Oeste do Paraná – UNIOESTE, approved by the Research Ethics Committee of UNIOESTE, with opinion n. 2,676,740, in which all participants signed the Informed Consent form, was inserted with the Brazilian Registry of Clinical Trials (REBEC) under TRIAL number: RBR-2SV9GW.

The sample was composed of 39 participants, of both genders (6 men), with a mean age of 20.6±3.7 years, body mass of 65.7±13.3 kg and height 1.67±0.09 meters. They were divided into four independent groups, one control group (CG) and three electrostimulation groups with variation in intensity (dose effect): one with intensity maintained at the contraction threshold (GT); another with intensity maintained 20% above the contraction threshold (G20); and another 30% above the contraction threshold (G30). The volunteers were randomly assigned to the groups by means of electronic randomization with the help of the resource available on the graphpad website.

The mean intensities of the currents applied to the samples of each group were 40.42±8.37, 48.73±10.47 and 50.12±12.48 mA for GT, G20 and G30, respectively.

Inclusion and exclusion criteria

Sedentary participants were admitted, with no disease or musculoskeletal lesion in the spine, aged between 17 and 40 years. We excluded individuals with uncontrolled systemic diseases, practicing physical activity systematically for at least twice a week, participants who interrupted the sequence of the intervention, in addition to the specific contraindications of the Aussie current.

Intervention

The intervention period lasted four weeks with three weekly sessions of 15 minutes each. In all electrostimulation groups, the Aussie current was used (Ibramed®, Amparo, Brazil), with the following parameters: base frequency of 1000 Hz, modulated at 50 Hz, the cycle presented a rise of 1 s, maintenance of 8 s, decay of 1 s and 10 s of rest. These parameters were fixed in order to analyze only the differences in current amplitude. The upper electrodes were positioned just below the last ribs and the lower electrodes were aligned with the upper posterior iliac spine (UPIS) at the level of the L5 spiny process. The electrodes used were rubber-silicone with 2x4 cm (Carci®, São Paulo, Brazil).

For the determination of the current dose, it was initially identified the intensity at which the contraction threshold was observed, characterized by visual inspection, at the beginning of a vigorous and sustained contraction, the percentage variations were based on this intensity.

Dependent variables

An initial evaluation (PRE) of the strength and stability of the deep muscles of the lumbopelvic region was performed, and the reevaluation (POS) occurred at the end of the interventions. Indirect measurements of strength and dynamic and static stability of the deep pelvic lumbar muscles were evaluated by a MioStab (Miotec®, Porto Alegre, Brazil) pressure biofeedback unit (PBU) (figure 1).[22]

Prior to the tests, the volunteers were familiarized and trained in the movements necessary to carry out the tests. Compensatory movements were corrected and avoided during the tests. In all the tests, the evaluated volunteers were placed in the dorsal decubitus position, with their arms extended along the body, knees flexed at 90º and feet supported on the stretcher. The PBU pres-

Fig. 1. Pressure assessment equipment. On the left is the MioStab equipment, with its bag and manometer. On the right the equipment in use, under the lumbar region of the volunteer

sure bag was inflated to the pressure established for each test and positioned horizontally and centrally in the region that comprises the last ribs and the UPIS. After positioning, the subject was asked to perform a forced respiratory cycle and, when necessary, pocket pressure was adjusted again.

For the evaluation of static stability, the pressure bag was under a pressure of 40 mmHg and the volunteer was instructed to breathe normally and, upon exhaling, to contract the muscles in an attempt to raise the navel towards the spine in order to promote a decompression in the pressure bag, due to the extension movement of the lumbar spine (with increased lumbar lordosis), keeping it away from contact with the bag. This decompression lasted 10 s. Three attempts were requested, with a two-minute interval between each of them, and the minimum pressure peak values were recorded during each contraction and for statistical analysis the mean value of the three attempts was considered. The test indicated good static stability when the contraction generated a pressure decrease in the bag of at least 6 mmHg and this decrease was sustained for at least 5 seconds.

For the evaluation of dynamic stability (that is, even performing movement with the lower limb, there would be the possibility of maintaining the pressure force), the pressure bag was with a pressure of 40 mmHg and the volunteer was instructed to breathe normally and, upon expiration, performed the abduction of one of the lower limbs (associated with external rotation of the hip, since the hip was bent, knees at 90o and feet supported by the stretcher), with the intention of touching the lateral face of the limb on the stretcher keeping the footrest in maximum possible amplitude, returning to the initial position after that. Three attempts were sought, with an interval of two minutes between each of them. In this test, the volunteer's ability to at least maintain the established initial pressure was evaluated. When the subject could not maintain the minimum pressure of 40 mmHg during the test, the dynamic stability was considered deficient.

For the indirect evaluation of the force, the pressure bag had a base pressure of 80 mmHg and the volunteer was instructed to breathe normally and, when exhaling together, to contract the muscles of the perineal and abdominal regions as intensely as possible in an attempt to bring the navel to the spine and promote a compression in the pressure bag. This contraction was sustained for as long as possible. For this evaluation only one attempt was requested and the inference of the force was based on the time of support of the contraction.

The control group participated in the initial evaluation and was reevaluate after one month, and electrostimulation groups were reevaluate in a period between one and seven days after the end of the session.

Statistical analysis

The SPSS 20 software was used for statistical analysis (IBM®, Armonk, USA). The significance level was 5% (α=0.05). The analyses were performed using Generalized Linear Mixed-effects Models (GLMMs) with Bonferroni post-hoc. The Effect Size was also analyzed by Cohen's d, using page https://www.estimationstats.com/#/, defined as <0.2: trivial; 0.2-0.5: small; 0.5-0.8: moderate; >0.8: large.

Results

Forty-one individuals were evaluated for eligibility, among them there were sample losses (n=2), 1 before randomization and 1 for not completing the intervention period, resulting in 39 volunteers in the final sample.

Regarding static stability of the multifids, it was found that there was no group effect (p=0.573) or interaction (p=0.606), but there was a significant difference in relation to the time of evaluation (p=0.002). By

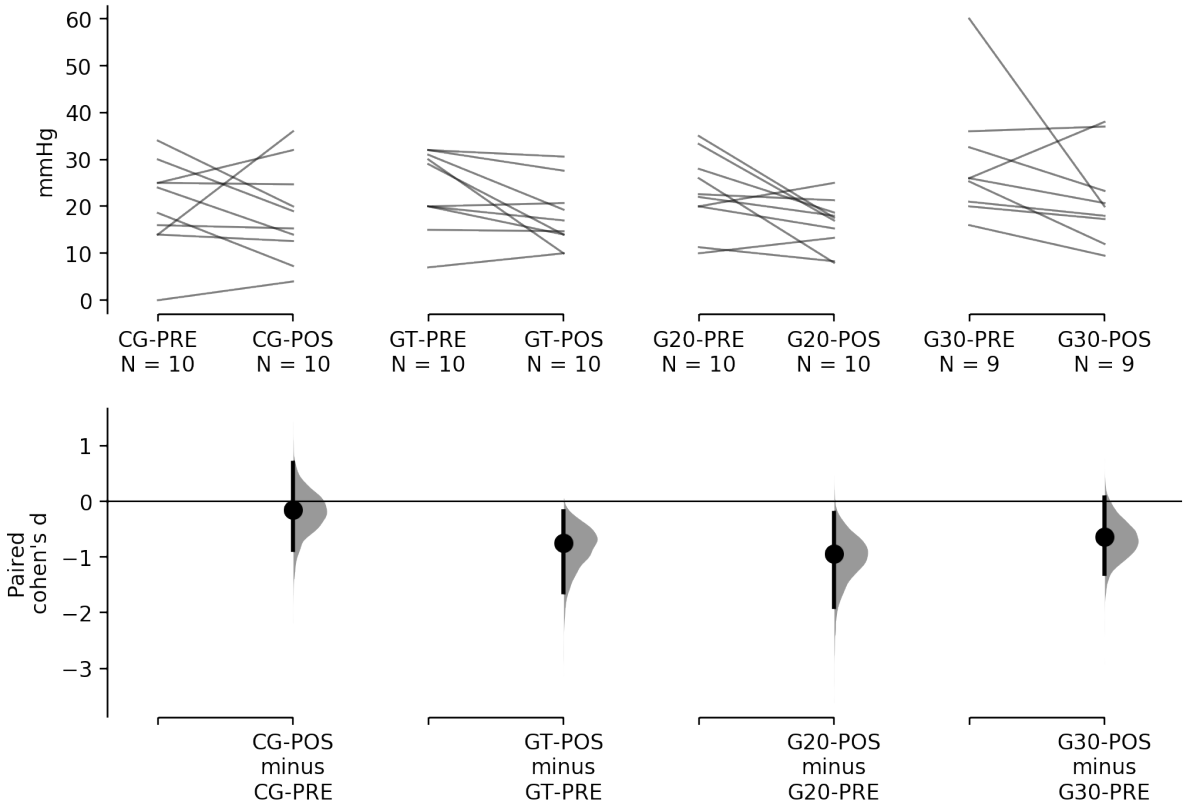

Fig. 2. Graphic demonstration of paired Cohen Effect Size d for the static stability of the multifidus. Raw data is plotted on the upper axes; each paired set of observations is connected by a line. On the lower axes, each mean difference is represented as a bootstrap sampling distribution. Mean differences are represented as points; 95% confidence intervals are indicated by the ends of the vertical error bars

analyzing the effect size, it was possible to observe that it was trivial for the control group (-0.16), moderate for GT (-0.75) and G30 (-0.64), and large for G20 (-0.95) (figure 2).

The second variable evaluated by the study was the indirect force with time as covariable, measured by the highest pressure peak and longest time contraction, acquired by the contraction of the abdomen transverse muscle. For this variable there was not any effect on comparisons between groups (p=0.363), moments (p=0.242) and interaction (p=0.839). The effect size found was considered trivial for GT (p=-0.04), small for CG (p=0.477), G20 (0.485) and G30 (0.346) (figure 3).

The third analysis of the study was linked to the evaluation of the contraction time. There were not any differences between the groups (p=0.230), but between the moments (p=0.041) and interaction (p=0.030). At the moment PRE the groups were similar, however, at the moment POS GT was higher than G20. Observing the moment, GT presented a significant increase comparing PRE and POS. Regarding the effect sizes, GC (0.259), G20 (0.382) and G30 (0.305) presented small effects, while GT (0.694) presented moderate effects (figure 4).

Discussion

In the present study, an increase in muscle strength and static stability of the multifidus muscles was obtained in the samples in relation to the moment PRE and POS intervention, regardless of the intensity that were submitted, however, there was no significant difference when compared between the groups, although different sizes of effect were found, which may point to practical differences, that is, clinical despite the lack of statistical differences.[23]

This result is contrary to the finding by Guirro, Nunes and Davini with the use of low and medium frequency currents in the quadriceps of healthy women for 5 consecutive days, for 3 weeks, for 30 minutes, with an interval of 24 hours between each application, in which the current intensity was increased to the maximum tolerance threshold and then there was an increase of 1 mA every 5 minutes of application.[24] The authors indicate that the increasing intensity caused an increase in the strength of the quadriceps of the samples. A hypothesis that can explain this contradiction is that the present study was based only on the muscular contraction threshold and not the maximum tolerance. This probably submitted the participants to intensities below the maximum tolerated. In addition, the cited article shows that at each session the intensity increased, being again

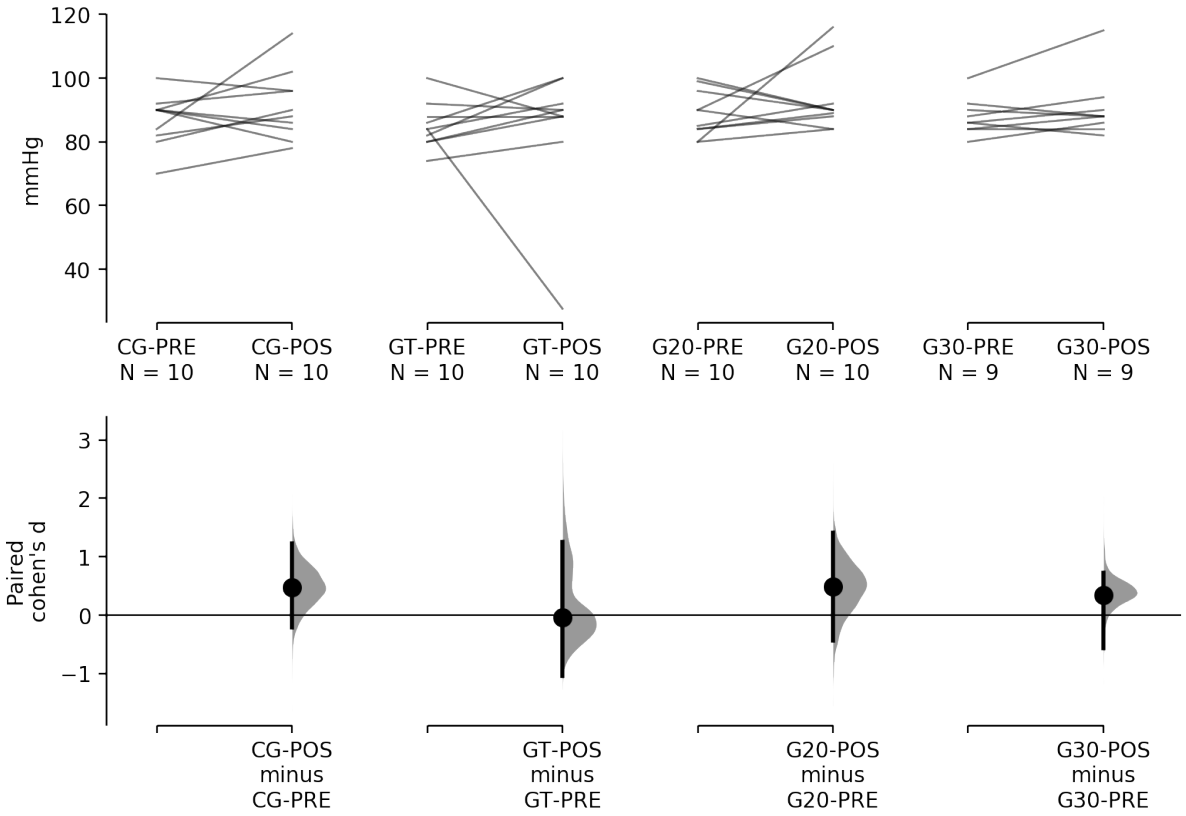

Fig. 3. Graphical demonstration of paired Cohen Effect Size d for indirect evaluation of dynamic stability. Raw data is plotted on the upper axes; each paired set of observations is connected by a line. On the lower axes, each mean difference is represented as a bootstrap sampling distribution. Mean differences are represented as points; 95% confidence intervals are indicated by the ends of the vertical error bars

different from the present study, in which the intensity did not increase between the sessions.

Marmon and Snyder-Mackler evaluated the dose-response curve in individuals after knee arthroplasty, and observed a significant correlation between current intensity with quadriceps force and voluntary activation.[19] Similarly, Almeida et al. used the NMES in individuals with rheumatoid arthritis, indicating for muscle strength gain, the use of intensities that produce between 15 and 50% of maximum voluntary contraction.[18] However, Hsu et al. reported that both low and high intensity NMES produce similar functional results in individuals with stroke.[21]

In relation to the increase in muscle strength of multifidus, Iijima et al. point out that the intensity of current affects muscle activation, influencing the recruitment of motor units during neuromuscular electrical stimulation.[25] This statement differs from the results obtained in this study, because the pressure peak did not show significant differences between the stimulated groups with different intensities, but it is noted that the sizes of the effect were greater than the control in the electrostimulated groups.

A systematic review aimed at pointing out the preconditions to generate a stimulus above the training threshold with NMES, pointed out that the choice of electrical parameters and the stimulation regimen are fundamental to obtain satisfactory results in force gain.[26] The authors related significant gains with stimulations above or equal to 50% of the maximum voluntary contraction of the individual, in addition, the values of frequency above 60 Hz, pulse duration between 200 and 400 μs and work cycle between 20 and 25% were important to optimize the results. The findings are in line with the results of the current study when considering the duration, both weighted on average, four weeks of training, with three sessions per week, but differs when analyzing the intensity, because in this study this effect was not evaluated. It is pertinent to highlight that the motivation and perception of discomfort of the individual may affect the ability to support higher intensities of stimulation, and consequently interferes in the results.

A current application with frequencies of several Kilohertz produce stimulation supra thresholds that are capable of producing multiple action potentials in the nerve fiber, producing long-lasting bursts that are adequate to maximize muscle torque.[25] This information is consistent with the results of a study that compared four different electric currents; two medium and two low frequency.[17] The authors points out that among them, the

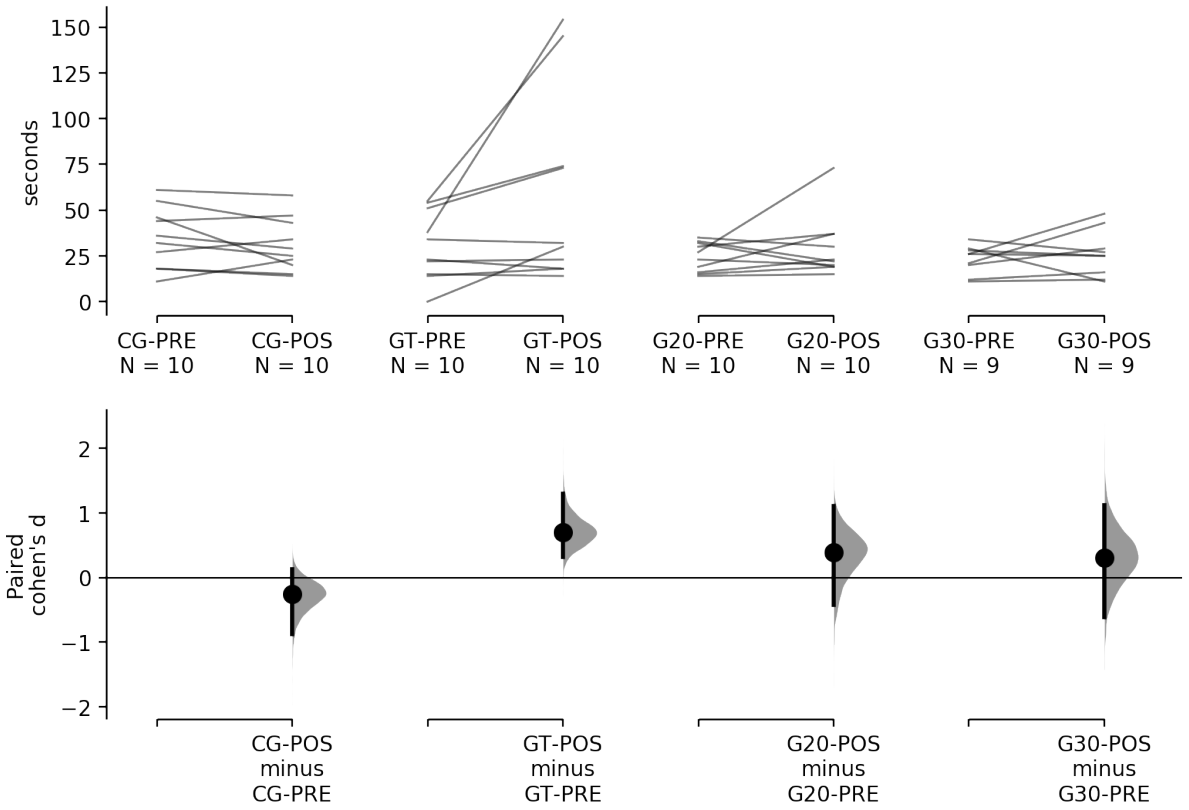

Fig. 4. Graphical demonstration of paired Cohen Effect Size d for the evaluation of contraction time. Raw data is plotted on the upper axes; each paired set of observations is connected by a line. On the lower axes, each mean difference is represented as a bootstrap sampling distribution. Mean differences are represented as points; 95% confidence intervals are indicated by the ends of the vertical error bars

Aussie current was the most effective in the production of knee extension torque. They also showed that NMES applied alone, was able to produce 66% of the maximum voluntary contraction torque, and although it is not a more effective method than voluntary exercise, NMES is able to produce more specific muscle fiber contraction than those activated by voluntary action; being an excellent supporting resource to strengthening programs for healthy individuals.

As for the variables analyzed, even with previous training, it is not possible to isolate a possible effect of motor learning in the procedures, generating an increase in mean values in the second evaluation, because all participants performed the evaluations, that is, they were taught to contract the muscle group studied, thus becoming aware of this contraction and the movements.[27] It is possible relate the unfavorable result of dynamic stability with the characteristic of stimulated muscles, because they are postural muscles, with this there was a significant increase in static stability. However, despite acting on pelvic stabilization during movement, it is not the only one that acts to generate dynamic stability, requiring a set of structures, such as the joints, neural system and various muscles (the main being the rectum and transverse abdomen, erector of the spine, multifidus and gluteus maximus), in addition, the multifidus have little biomechanical advantage, precisely because they are postural muscles, serving as decelerators of movement.[10,28] Since one of the limitations of this study was the absence of electroneuromyographic evaluation of the multifidus, it is not possible to discriminate only their action on the tests performed.

Another hypothesis may have been related to the training method, in which the stimulation was performed in a neutral position, in ventral decubitus, stimulating in only one degree, not having a dynamic training. This can be considered another limitation in the present study and suggestion to be addressed in future researches.

Conclusion

The results obtained indicated that the Aussie current has conditions to produce a strengthening of the lumbar multifidus muscles, generating static stability of the lumbar-pelvic region. However, the dose used in the different stimulated groups did not promote significant difference.

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ORIGINAL PAPER

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Discharge against medical advice at the adult accident and emergency department in a tertiary hospital of a developing nation

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ABSTRACT

Introduction. The goals of health care provision include that it be accessible, acceptable, affordable and adequate. Discharge against medical advice (DAMA) is a failure of proper health care provision as there is disagreement arising from dissatisfaction with provided health care. DAMA is common in our sub-region because of many reasons; these includes ignorance, financial constraint of the patient, beliefs in unorthodox care and patients feeling that they are well when their caregivers do not think so.

Aim. The objectives of this study are to determine the incidence, method of documentation of DAMA in the case notes and patients reasons for DAMA in our tertiary health institution. The A&E of any hospital in our environment attracts public criticism when there is dissatisfaction with services and DAMA when not handled well can lead to justifiable criticisms and/or litigations.

Material and methods. This is a retrospective study. It was carried out at the adult accident and emergency department of Enugu state university of technology teaching hospital Enugu. Duration of the study was from January 2017 to December 2018.

Results. A total of 8,152 patients were seen in the accident and emergency during this period. One hundred and seventy one (171) case notes were retrieved and reviewed for the study, DAMA rate of 2.1% was obtained. Fifty one folders (29.8%) did not have reason for the DAMA documented in them. The commonest reason for the DAMA was to seek traditional medical care with frequency of 17.5%. This was closely followed by financial constraint with 15.8%. Documentation for DAMA was done directly in the case notes.

Conclusion. The incidence of DAMA from this study is similar to what is obtainable from other local studies, financial constraint on the patients and seeking alternative medical treatment were the commonest reasons for DAMA in our sub-region. Also, the documentation for the DAMA in this study was poorly done.

Keywords. accident and emergency, alternative medical treatment, discharge against medical advice, financial constraint, National Health Insurance Scheme (NHIS)

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Introduction

Patients discharging against medical advice is commonly encountered in many hospitals in our sub-region. Discharge against medical advice (DAMA) is when a patient discharges from the hospital or health care facility before the treating physician recommends discharge.[1] This implies that the patient or his/her custodian withdraws the consent given to the medical personnel to offer his/her services on the patient.[2] This decision is an informed one that can only be taken by a mentally sound adult.[3] Discharge against medical advice is of concern because it is assumed that these patients are leaving too soon and that adverse consequences may follow. Research has shown that mortality rate of patients discharged against medical advice increased.[4] Also DAMA is one of the leading causes of hospital readmission.[5,6] The increased readmission rate may be due to deterioration in the patient's condition at home or cessation of the treatment before stabilization of his/her health condition.[7]

Patients have the right to leave an accident and emergency department against medical advice based on human rights and the patient's charter.[8,9] In the exercise of such right by patient, medical staff must avoid deficiencies in compliance to DAMA process as they may be held liable in the event of morbidity or mortality.[9]

Lawsuits related to discharges are more common among those that discharged against medical advice, in recognition of this, hospitals should put up measures to ensure that the discharge against medical advice process is properly documented through provision of proper forms.[10] Well executed DAMA forms have been found to protect physicians against litigation and indeed will be a useful and compelling piece of evidence to help establish a defense for the physician from any liability in any civil suit which may be instituted against him/her.

The prevalence of DAMA is higher in developing nations. Some of the reported reasons for DAMA includes perceived improvement in clinical state or preference for alternative therapy like traditional bone setters, low levels of the followings: trust, partnership and communication between patients and their doctors. Other reasons are financial problems, and dissatisfaction with the hospital environment.[7,12-14]

There had not been a study on the reasons for discharging against medical advice in this centre, the study will help to reveal reasons for this irregular discharges.

Aim

The objectives of the study are to determine the incidence of DAMA, method of documentation of DAMA in the case notes and reasons for discharge against medical advice in the adult accident and emergency department of Enugu state university of technology teaching hospital.

Material and methods

The study was carried out at the adult accident and emergency department of Enugu state university of technology teaching hospital, Enugu. This facility cares for adult medical, surgical and gynecological emergencies. Duration of the study was from January 2017 to December 2018. Enugu state university teaching hospital is one of the three tertiary health facilities that offer care to the residents of Enugu and its environs. Enugu is one of the oldest states in Nigeria. It has a geographical coordinates of 63oN and 73oE and has a population of 3.3 million people with a population density that is thrice the national average according to national census figures of 2006.

Study design

A retrospective study that was mainly observational and descriptive in nature.

Study location/facilities

nugu state university of technology teaching hospital lies along highway 343. The A & E has 16 beds in the adult accident and emergency department with almost 100% bed occupancy rate. The hospital is located within Enugu metropolis in the city center. There are 2 consultant orthopedic surgeons, assisted by senior medical officers, junior resident doctors, nursing and other adjunct staff. The facility resuscitates patients and share subsequent care with other hospital units. The theater facility can handle minor injuries only and the hospital main laboratory and radiology units serve the A&E.

Study duration

The study duration was 2 years, from January 1st 2017 to 31st December 2018.

Inclusion criteria

All the patients, 18 years and above that discharged against medical advice within the study duration.

Exclusion criteria

Patients below 18 years of age and those whose case records were incomplete.

Procedure/methodology

Ethical clearance was obtained from the hospital ethical committee, case notes of all the patients that presented to the accident and emergency and subsequently discharged against medical advice within the study period were retrieved for the study. We also consulted the ward records, and the statistics unit of the medical records department. The data collected were reviewed for patient's basic demographic characteristics which include the age, sex, duration of admission, the clinical diagnosis, reasons for the DAMA and method of administration of DAMA.

Statistical analysis

The data obtained was analyzed using IBM-SPSS version 22 for simple averages and measures of statistical tendencies.

Results

A total of 8,152 patients were seen in the accident and emergency during this period. One hundred and seventy one (171) case notes were retrieved and reviewed for the study. Male to female ratio is 1.6: 1. The age range with the highest frequency of DAMA is 21 – 30 years. The frequency distribution in other age-groups is as documented in the table 1 below. The patients were categorized according to the unit that attended to them. Orthopaedic unit has the highest frequency of DAMA with 40 patients (23.4%). The second commonest unit was cardiology with 22 patients (12.9%). The units and their frequencies are as shown in table 2.

Table 1. Age group of patients and their frequency

	Frequency	Percent
Age group		
≤20	13	7.6
21 – 30	69	40.4
31 – 40	33	19.3
41 – 50	18	10.5
51 – 60	11	6.4
61 – 70	11	6.4
>70	16	9.4

Table 2. Frequeny of DAMA by units

Department	Frequency	Percent
Ophthalmology	3	1.8
Urology	11	6.4
Orthopaedics	40	23.4
Cardiology	22	12.9
Obs & Gynae (including rape 2 cases)	14	8.2
Gen surg	3	1.8
CTU	4	2.3
Plastic Surg	18	10.5
Neurosurgery	17	9.9
ENT	1	0.6
Psychiatry	1	0.6
Endocrinology	3	1.8
Neurology	3	1.8
Gastroenterology	13	7.6
Resp Medicine	15	8.8
Hematology	3	1.8

Fifty one folders (29.8%) did not have reason for the DAMA documented in them. The commonest reason for the DAMA was to seek traditional medical care, this was seen in 30 patients (17.5%). This was closely followed by those that discharged as a result of financial constraint. The reasons for DAMA are shown in table 3. There was no formal DAMA form available in the accident and emergency department. The patients just document and sign in the folder that they want to be discharged against medical advice.

Table 3. Reasons for DAMA

Reason	Frequency	Percent
No comment	51	29.8
To seek alternative medical care	30	17.5
Financial constraint	27	15.8
Not satisfied with care/delay in treatment	13	7.6
Feeling that they are well	17	9.9
Another hosp	16	9.4
Ignorance, do not want to sleep over in the hosp	14	8.2
Went to prayer house	3	1.8

Discussion

Generally, hospitals in developed nations observe a low DAMA rate. This is reflected in the incidence reported by various authors. Pennycook et al. reported a DAMA rate of 0.73% in their Accident and Emergency department in their study in the united kingdom.[15] Wong et al. in a similar study reported DAMA rate of 0.95%.[16] Udosen et al. in their study in south-south Nigeria obtained DAMA rate of 2.6%, Oguzie et al in a local study obtained a rate of 1.6%.[17] Value of 2.1% obtained from this study is not far from values from other local studies. The lower rate of DAMA reported from developed nations may be caused by much more encompassing health insurance policy in developed nations which takes care of total cost of treatment, this contrasts with what is obtainable in many developing countries and that is why one of the major reasons for DAMA in developing countries is financial constraint on the part of the patient.

There is male preponderance from this study, this is consistent with what was reported by Pennycook et al. in the united kingdom.[15] This may be due to overall majority of male patients who are involved in trauma cases.

Furthermore, from this study, all the patients that sought for discharge against medical advice or their next of kin documented directly in their case notes stating that they do not wish to continue treatment in the medical facility. Standard DAMA forms were not available hence the documentations were not uniform. The reason for the DAMA was not documented in 29% of the case notes. Poor documentation was also reported by previous authors.[9,18,19] This shows that health care workers probably paid little attention to the details in DAMA processing and probably are overtly reliant on the signature of the patient as a reason to be exonerated from legal penalties in the event of litigation.[9] This is a cause

for concern because it may leave room for culpability in matters of legality where a detailed DAMA audit is required. Documentation of DAMA must be meticulous, the American College of Emergency Physicians suggests that every chart should reflect that the patient is competent and understands the diagnosis, treatment offered, alternative therapy and potential consequences of disregarding the recommended treatment.[20]

Results from this study shows that patients with orthopaedic problems have the highest rate of DAMA, 23.4% of the patients. This is similar to what was reported in separate local studies by Ohanaka et al. and Oguzie et al.[21,22] Also the commonest reason for DAMA from this study is seeking alternative medical treatment, Ohanaka et al. in their separate articles also documented seeking alternative medical treatment as the commonest reason for DAMA.[21] This may be due to the belief among the populace that fractures are better managed by traditional bone setters. This belief is disputed by high rate of complications among those that patronize these practitioners[21]. High patronage of traditional bone setters may also be connected to the cheap and affordable services the patients feel they receive from them.

Financial constraint on the part of the patients is the second commonest reason for discharge against medical advice in this study. Several authors including Jimoh et al., and Oguzie et al., mentioned financial constraint as the main reason for discharge against medical advice.[22,23] This is definitely as a result of the prevailing harsh economic condition in Nigeria, coupled to limited coverage of the NHIS, this seriously impairs the capacity of the individual to finance his/her healthcare. Jimoh et al. in their article mentioned other reasons that can lead to DAMA.[23] These are dissatisfaction with management plan, tiredness of staying in the hospital, feeling of reasonable recovery and ineffective communication between the attending doctor and patient. Some of these reasons were also obtained from this study. Pennycook et al. reported that it is probable that an unfriendly welcome to A and E unit, rude medical and nursing staff and above all, a prolonged waiting time are likely to increase the number of irregular discharges.[15] All these factors may contribute to an apparently unreasonable, angry patient who may be covertly encouraged to leave by a member or staff. A study that was carried out in Kuwait mentioned dissatisfaction of the patients who received care at the hospital as the main reason for DAMA.[24] From the above, it can be observed that majority of the studies carried out in low income countries mentioned seeking traditional medical care and financial constraint as the major reason for DAMA while studies done in high income countries tilted towards patients dissatisfaction with treatment and unfriendly environment in the accident and emergency as the major reason for DAMA.

The incidence of DAMA from this study is similar to what was obtained from other local studies, however studies from developed countries shows lower rate of DAMA. Financial constraint on the patients and seeking alternative medical treatment were the commonest reasons for DAMA in our sub-region. Also, findings from this study shows that the documentation for the DAMA was poorly done.

More effort need to be focused on proper documentation in administration of discharge against medical advice to patients. DAMA form should be made available to the accident and emergency department which should be signed and witnessed in cases of discharge against medical advice, this will minimize any subsequent medicolegal problems for the attending doctor and accident and emergency department. Also positive measures are required to minimize the numbers of patients leaving prior to their medical care being completed, firstly prompt friendly and professional clinical evaluation of all patients presenting to the accident and emergency with a written record on the accident and emergency card should be undertaken. Any attempt at early departure should be courteously and sympathetically met with a reasoned explanation, preferably by a member of the medical staff of the importance of completing treatment. A more encompassing NHIS will surely take off the financial burden from the patients, this will eliminate discharge against medical advice as a result of financial constraint on the patient.

Conclusion

A major limitation to this study is incomplete documentation in the case notes for the patients that are discharging against medical advice, reasons for the discharge were not written in case notes of a lot of the patients. Subsequent prospective study is recommended for more accurate findings.

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ORIGINAL PAPER

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Genetic study of a family with affected members with Waardenburg syndrome type 4 without Hirschsprung disease

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ABSTRACT

Introduction. Waardenburg syndrome (WS) is an autosomally inherited disorder with the most common state compounding pigmentary abnormality and sensorineural deafness. The rarest type of the disease is WS4 with the general characteristic discriminated from other types by the attendance of Hirschsprung disease (HD). Among the several genes, one of the causative genes in WS4 is endothelin 3 (*EDN3*) with both autosomal recessive and dominant inheritance.

Aim. The intention of the present study is to report a pathogenic mutation as the genetic cause of WS in an Iranian family with four patients without any segregation criteria for the type of the disease.

Material and methods. In order to detect of causing gene or genes related to the disease, Whole exome sequencing (WES) technique in proband's sample was done. To confirm the detected mutation in proband and some family members with or without the disease direct sequencing of *END3* gene was performed using Sanger method.

Results. Pedigree analysis suggested segregation of WS as an autosomal recessive trait in the family. WES analysis suggested a gene (*EDN3*) related to WS type 4B. DNA sequencing confirmed a pathogenic missense mutation c.293C>T, p.T98M in *EDN3* gene in all of the four patients.

Conclusion. Determination of WS can usually be missed owing to the lack of some attributes in every sufferer and also conventional clinical variance, in spite of several affected members in a single family. So, Genetic counseling is pivotal for families with multiple members influenced. We detected c.293C>T, p.T98K mutation in *EDN3* gene as a pathogenic variant which has been known as a likely pathogenic state in the American College of Medical Genetics and Genomics (ACMG) guidelines, despite one prior report. It will be helpful in genetic diagnosis of affected persons and increases the mutation spectrum of *EDN3* gene.

Keywords. *EDN3* gene, Waardenburg syndrome, WS4

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Introduction

Waardenburg syndrome (WS) is an infrequent autosomally inherited disorder with varying circumstance and a prevalence of 1 in 40,000 resulting from the nonexistence of melanocytes in the skin and the striavascularis of the cochlea.[1] Indeed, the anomalous proliferation, survival, migration, and distinction of pluri potent neural crest cells of the neural tube in the course of embryogenesis has been ascertained as the reason of the clinically disparate attributes in particular the absence of melanocytes of the skin and inner ear.[2] In general, WS is a sort of syndromic hearing loss which explicates 2-5% of the patients with congenital deafness and 0.9-2.8% of the deafness patients.[1] WS described by achromia (lack of typical pigmentation), such as depigmented speckles of the skin and hair (white forelock or white hairs and patches in other sites on the body), iris melanocytic malformation, bright blue eyes or Heterochromia irides, and sensorineural hearing loss (SNHL), most often non advancing, varying from slight to profound. Therefore, WS have been observed as a disease with variable penetrance.[3] WS is the most common state compounding pigmentary abnormality and sensorineural deafness. In the most of cases, bilateral ear affection turns up although in scarce cases it occurred unilateral.[4] Based on the further symptoms, it has been categorized into four subtypes, including WS1 (OMIM: 193500) with dystopia canthorum, WS2 (OMIM: 193510) without dystopia canthorum, WS3 (OMIM: 148820) with dystopia canthorum and extra musculoskeletal abnormalities, and WS4 (OMIM: 277580) with added Hirschsprung's disease (HD) (OMIM: 142623) or chronic intestinal pseudo-obstruction.[5] Among which WS1 and WS2 are the most common and WS4 is the rarest type with an incidence of <1/1,000,000 live born infant. WS4 (furthermore, known as Waardenburg-Shah Syndrome) with general characteristic including hereditary sensorineural hearing loss, Heterochromia of the eyes, white forelock, melanocytic deficiencies of the hair and skin is discriminated from other types by the attendance of HD.[6] Owing to the expression of various genes have been occurring the discrepancy in the medical appearance of the disease. So far, at the molecular status, six pathogenic genes with variable rates of occurrence are implicated; Paired box3 (*PAX3*) is connected with types 1 and 3, melanocyte inducing transcription factor *(MITF)* and snail family transcriptional repressor2 (*SNAI2*) with type 2, *EDN3* and endothelin receptor type B (*EDNRB*) with type 4, and SRY-box transcription factor10 (*SOX10*) gene with types 2 and 4. All six genes are involved in a complex interaction related to the function of melanocytes (pigment-producing cells). Dysregulation of them results in abnormal development of neural crest cells; whereby, changes in the pigmentation of the ears, iris, hair, and skin.[7] Based on the genetic causes, WS4 is classified into three subtypes: 4A, 4B induced by *EDNRB* and *EDN3* gene mutations with hereditary an autosomal recessive manner, individuals carrying homozygous mutations manifesting WS4 and those with heterozygous mutations in either gene presenting with isolated HD, and 4C with mutation in the *SOX10* gene that is inherited in an autosomal dominant manner. In truth, these genes are engaged in the formation and development of numerous kinds of cells, and are crucial constituents of a signaling cascade that controls the progression of melanocytes and the enteric nervous system.[8] Pathogenic variations in any of these genes disrupt ordinary development of melanocytes, altering pigmentation of skin, hair, eyes, and the normal functioning of the inner ear result in sensorineural hearing deterioration.[9] Endothelins (*EDN*) are a family of three active peptides *EDN-1*, *EDN-2*, and *EDN-3* that deed as ligands and exert their effects by binding to a G-protein heptahelical receptor known as endothelin receptors (*EDNR*) involved in the development of neural crest cells, which engenders the enteric nervous system and melanocytes. Two sorts of *EDNR* are determined; *EDNRB* which binds all three peptides and *EDNRA* which selectively binds *EDN1*. The significance of *EDN3*/*EDNRB* ligand/receptor interplay for the development of two varied cell lineages, melanocytes and enteric neurons, originate from the neural crest is well acknowledged.[10] Endothelin mRNAs are first translated into preproendothelin, which undergoes two step enzymatic cleavages, proteolytic cleavage of the prepro-endothelin by furin enzyme to release pro-endothelin and then converted into mature active by endothelin-converting enzyme (*ECE-1*) that produces the mature active endothelin peptide. This small peptide with 21 amino acidsis stabilized through the formation of two disulfide bonds between cysteine residues four contains cysteines involved in two disulphide bonds. [11]

Aim

The intention of the present study is to report a pathogenic mutation as the genetic cause of WS in an Iranian family with four patients without any segregation criteria for the type of the disease.

Material and methods

Clinical characteristics and family history

Two asymptomatic parents were referred to our Genetic laboratory for genetic counseling and diagnosis of their affected child, the first son of consanguineous healthy parents, who was a 2-year-old symptomatic Iranian boy with a profound congenital hearing loss, which was treated successfully with a cochlear implant, blue-colored irises, and other pigmentary deficiency; for instance, pigmentation on his face. His parents were healthy with typical hearing, eyes, and skin. Based on

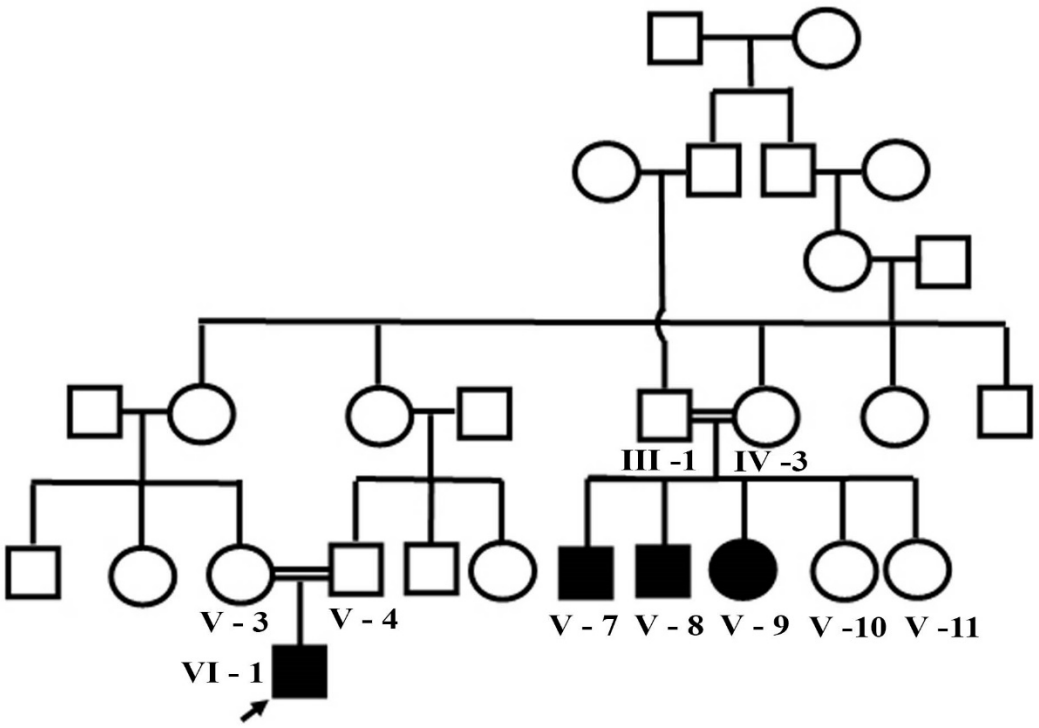


Fig. 1. Pedigree chart of the family with WS4. The black and unfilled shapes represent affected and unaffected family members, respectively; squares represent males and circles represent females; The black arrow indicates the proband (VI-1); V-3 and V-4 are the proband's parents; V-7, V-8 ,and V-9 another affected persons in the family in fifth-generation; V-10 and V11 unaffected sisters in 5th generation

the clinical/Para-clinical investigations the referring physician suggested WS as a possible diagnosis for him without any discriminate criteria for the type of the disease. According to the family pedigree, the affected child was born from a first cosines marriage. Also, there were multiple cases with the same presentations in the pedigree in the 5th generation of this family; two affected males and one female with exact same clinical symptoms compared to the proband, such as hearing impairment (Figure 1).

Each of these affected individuals was referred to a relevant physician for monitoring of clinical manifestations and other further investigations. After confirming the indications of the disease in all patients including a 25-year-old women with depigmented patches on her skin, white forelock, bright blue eyes and two 35 and 40 year-old man with equivalent symptoms (Figure 2); addition to, premature graying of the hair observed since birth. Relied on radiological examinations, none of the members in this family in particular the patients presented any colonic aganglionosis and similarly in accordance with the discriminator criteria of diverse types of WS, so four patients did not accord with the any especial type.

In general, the parents of the proband and the three other patients further their healthy sisters were participated in the study and whole blood samples were gained for next molecular investigations. Written informed consent was obtained from all of the individuals contributed in this genetic research.

Mutational screening

WES (Whole exome sequencing)

In order to detect of causing gene or genes related to the disease, WES technique in the proband's sample was done. For this purpose Genomic DNA was extracted from whole blood of him using standard protocols. Human whole exome enrichment was performed using Twist Human Core Exome Kit and the library was sequenced on the Illumina platform with a raw coverage of 199X and mean on-target coverage of 63X. Nearly all exons and flanking 10bp were detected and analyzed. Detected variations include single point mutations, and small insertions or deletions (indels) within 20bp.

PCR and Sanger sequencing

For corroboration of the detected variant in the proband and the inspection of it as a possible cause of the disease in other affected persons in the family, the revealed mutation was screened in parents of the proband; in addition, three affected persons and their two unaffected sisters by directly Sanger sequencing method. Genomic DNA was extracted from blood samples using a commercial kit (**GeneAll Exgen**$^{e\text{TM}}$), according to the manufacturer's protocol. For PCR amplification and direct sequencing of the detected gene two oligonucleotide primer

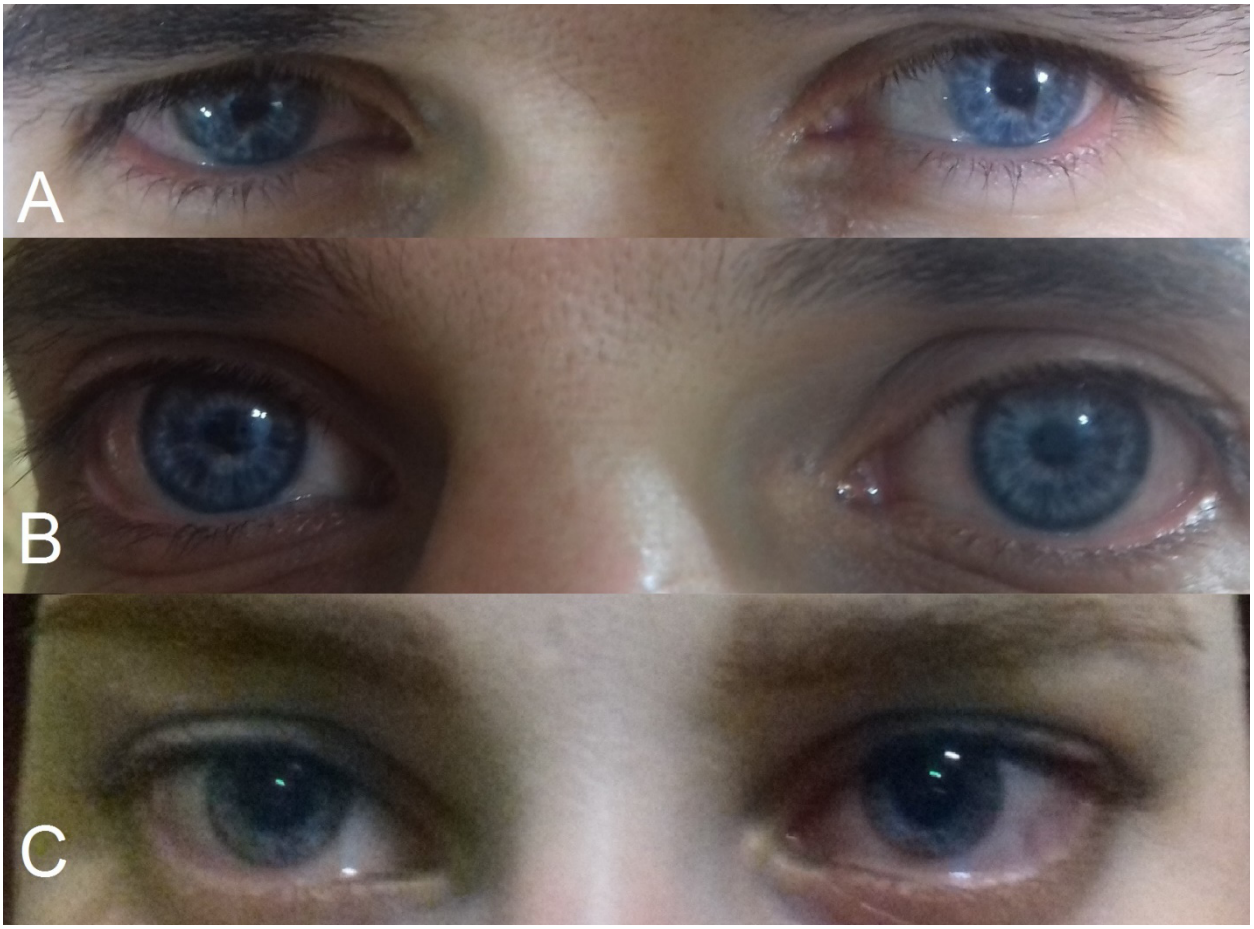


Fig. 2. Clinical features of the affected individuals with bilateral hearing loss and also bright blue eyes as the clearest characteristics. A, B, and C: Partial facial photograph of affected individuals V-7, V-8, and V-9

pairs were designed, including forward 5-'ATAGCTTG-GAAACTTTTCAGAAACTG-3' and Reverse5'-TG-GTCAGTTCACTTCATTCAGAG-3'. The amplification reaction was set in a total volume of 25 µl; containing 12.5µl PCR master mix (Yekta Tajhiz Azma, Iran), 1µl of each described primers, 8.5µl H2O, and 2µl DNA samples. The reaction was performed in initial denaturation at 95°C for 5 min, 35 cycles at 95°C for 30 sec, 60°C for 1 min and 72°C for 90 sec, and final extension step of 72°C was conducted for 7 min on a thermal cycler (Veriti, Applied Biosystems, USA). The PCR products were analyzed on 2% agarose gel before sequencing. The products sequenced on ABI 3500 Genetic analyzer. Subsequently, the similarities between the obtained sequences and the reference sequence were evaluated using the Nucleotide-Nucleotide BLAST (blastn) tool. Miscellaneous lines of in silico computational analysis (Mutation Taster, CADD, Poly phen, Varsome, SIFT, etc.) were made use to augur pathogenicity of the variation.

Results

WES was used to scrutinize all genes known to be responsible for hearing loss, including the WS pathogenic genes *PAX3*, *SOX10*, *MITF*, *EDNRB*, *EDN3*, and *SNAI2*, owing to the proband's clinical manifestations. Analysis of exome data, showed three variants as possible candidates that may explain the clinical history of the proband (Table1).

The detected heterozygous missense variant in tenascin C (*TNC*) gene has not been previously reported for its pathogenicity. Prediction of computational tools was conflicting. MutationTaster, CADD, and SIFT supported the deleterious effect of the variant on the gene or gene product(s), while Poly Phen has predicted it as tolerated/benign. The variant is absent in population databases (ExAC, 1000G, and our local database). Based on ACMG guidelines, this variant has been classified as a Variant of Uncertain Significance (VUS).

The detected heterozygous missense variant in tectorin alpha (*TECTA*) gene has not been previously reported for its pathogenicity. Prediction of computational tools was conflicting. MutationTaster and CADD has supported the deleterious effect of the variant on the gene or gene product(s), while SIFT and Poly Phen has predicted it as tolerated/benign. The variant has very low frequency in population databases (ExAC, 1000G, and our local database). Based on ACMG guidelines, this variant has been classified as a VUS.

Table 1. All data were derived from UCSC Genome Browser. Het: Heterozygous, Hom: Homozygous, OMIM number: Five-digit number assigned to each phenotype in Online Mendelian Inheritance in Man (OMIM) database. AR: Autosomal recessive, AD: Autosomal dominant, VUS: Variant of Uncertain Significance. Based on American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants [1]

Gene / Transcript (RefSeq)	Variant Location	Variant	Chromosome Position	Zygosity[1]	Related Phenotypes	OMIM number	Inheritance Pattern	Variant[1] Classification
EDN3 NM_207034.3	Exon 2	c.293C>T p.T98M	Chr20: 57,876,705	Hom	Waardenburg syndrome-type 4B	613265	AR/ AD	Likely pathogenic
					Congenitalcentral hypoventilation syndrome	209880	AD	
TNC NM_002160.4	Exon 2	c.346G>A p.A116T	Chr9: 117,852,952	Het	Autosomal dominant deafness-56	615629	AD	VUS
TECTA NM_005422.2	Exon 7	c.1682G>T p.G561V	Chr11: 120,996,489	Het	Autosomal dominant deafness-8/12	601543	AD	VUS
					Autosomal recessive deafness-21	603629	AR	

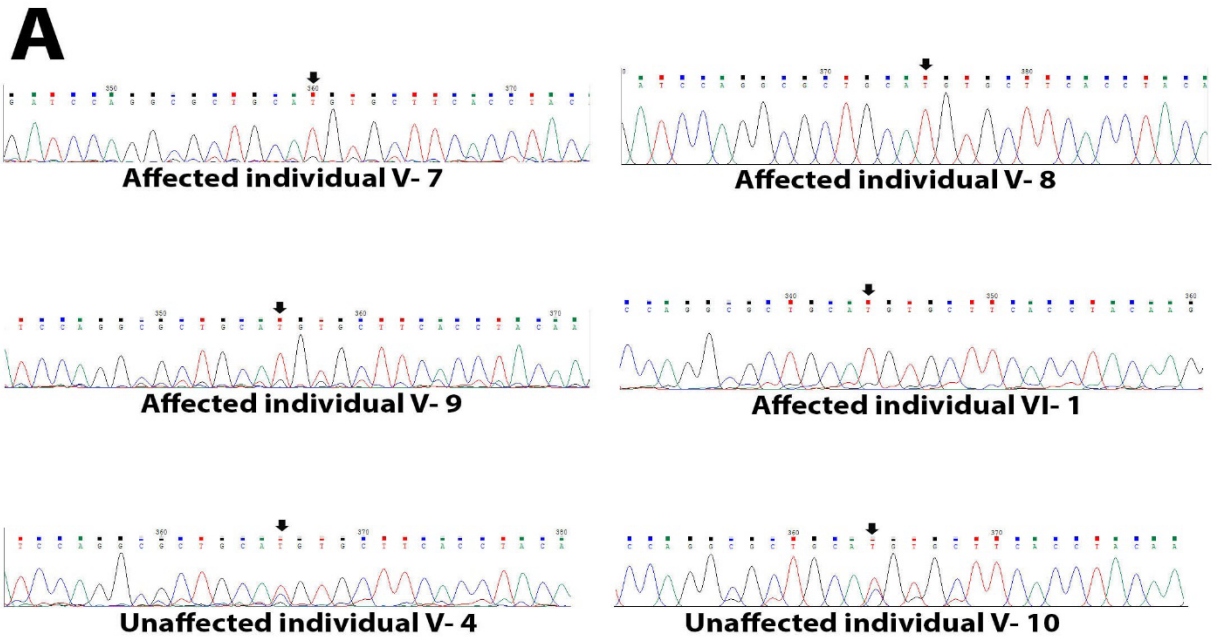
The detected homozygous missense variant in *EDN3* gene has been reported in Human Gene Mutation Database (HGMD) as a pathogenic variant. Moreover, the HGMD has reported another missense variant at this amino acid position (c.293C>A, p.T98K) as a pathogenic variant. Multiple lines of in silico computational analysis (MutationTaster, CADD, etc.) have been supported the deleterious effect of the variant on the gene or gene product(s). The variant is absent in population databases (ExAC, 1000G, and our local database). Based on ACMG guidelines, this variant has been classified as a likely pathogenic variant.

On the basis of the heterozygous status of detected variant in *TECTA* gene, this variant could not be explained the proband's deafness phenotype which had an autosomal recessive state. However, the possibility of large deletion/duplications and existence of a second causative variant in untested regions (introns, UTRs, etc.) of this gene could not be ruled out. On the other hand, *TNC* and *TECTA* genes were associated with autosomal dominant conditions, but analysis of detected variant in *EDN3* gene rejected the role of them resulting in their autosomal dominant conditions.

The same mutation, c.293C>T (p.T98M), on *EDN3* gene was detected in a homozygous state in the proband and three other affected members of the family, as a result of Sanger sequencing. The similar mutation, c.293C>T (p.T98M), on *EDN3* gene was detected in a heterozygous state in patients' Parents and also one sister of affected members in 5th generation of the family. Another sister was normal without any mutation in this variant of the gene (Figure 3).

Discussion

We are reporting a mutation in *EDN3* gene (causing gene in WS4) carried in the homozygous state by three men and one woman in a family. The observable assessing of the family suggested the WS disease as an autosomal recessive trait (based on family pedigree) and the molecular results revealed a likely pathogenic (Based on ACMG guidelines) homozygous substitution mutation, c.293C>T in exon 2, changing codon position 98 from threonine to methionine (p.T98M) in the proband (VI-1). It was possible to assume this variant as the causative variant in the proband and confirm diagnosis, but due to the likely pathogenic classification of the variant further examination (such as checking other members of the family) confirmed pathogenic nature of this variant. It could be used in definitive diagnosis. Furthermore, Genetic counseling and investigating the detected variant in *EDN3* gene in patients' parents and other members of his family/pedigree, especially affected members, were done. The affected family members (V-7, V-8, and V-9) were also homozygous for the mutation. Both parents of the proband (V-3/V-4) and other patients (III-1/IV-3) were heterozygous. Inspections in two normal siblings of three patients in fifth-generation (V-10, V11) showed the heterozygous variant in V-10 and wild-type allele in another sister. The c.293C>T change in *EDN3* gene were reported previously in an affected boy in an Indian family as a causing mutation of the WS4. The results of this research revealed a novel homozygous substitution mutation in *EDN3*. According to the Mutation Taster, the mutation was predicted to be disease causing with a p-value (probability) of 0.52. They also used two other in silico methods, PolyPhen-2 and SIFT, to see the effect of this mutation on the protein function. The effect of this mutation on *EDN3* was predicted to be probably damaging and intolerant with a score of zero (score ranges from 0 to 1, where 0 is damaging and 1 is neutral) and a score of 1 (score ranges from 0 to a positive number, where 0 is neutral, and a high positive num-



B

GCAGAAAGTATGCAAAATGCATGCAAGTTTTCAACGGGTGCAGATAGCTTGCAAGCTTTTCACAGAGTGT
GCAGATAGCTTGGAAACTTTTCAGAAACTGCGCAGAGCTTTGGAAACTTTGCAGACATTTTGCTTGCTCC
ACCCCCCTCCTCAGGTGTTTGGGGGTGGCGGGTGTTGAGGGGTCTGCACACTCAGCTTAGGAGCCCCTCA
ATCTGCCTTCTGCAGGATTCGTGCCTTGCTCCCAGTCTGGGGATGCTGGCAGGCGCGGCGTGTCCCAGGC
CCCCACTGCAGCCAGATCTGAGGGGGACTGTGAAGAGACTGTGGCTGGCCCTGGCGAGGAGACTGTGGCT
GGCCCTGGCGAGGGGACTGTGGCCCCGACAGCACTGCAGGGTCCAAGCCCTGGAAGCCCTGGGCAGGAGC
AGGCGGCCGAGGGGGCCCCTGAGCACCACCGATCCAGGCGCTGCACGTGCTTCACCTACAAGGACAAGGA
GTGTGTCTACTATTGCCACCTGGACATCATTTGGATCAACACTCCCGAGTAAGTCAGCCTTTTGTGGTGA
GGAACGTGGCTCCCGGACCAGGCCCACATCTGCTCATTCCCAGGAGGACCTCACTCCACCCCAGCCCCGC
TCAGTTAGCCCAGAGCCTGCCCTGGCACAGCCTTTAGCTCTTGCTGGGGCCTCTTGCCAGCCCAGGTCTC
TTCTGCAGGTCAGGGGTGTGACCCACATCCCCCCTGAGGGCCTGGCCCAAGAGAAACTCAATCCTGAGTT
TGATCCTGTGGAAGGAGGAGCCCTCCCTCTGAATGAAGTGAACTGACCAGGGGGATTAGATACCTGAGAT
GTCTCTCTGAGCCTCTTTTCTGAGATAGAGAAAGCCCCGAAAGTTTATCTCATTCCCCAGGGGCCAAGGG

Fig. 3. Mutation screening of the EDN3 gene in the family. A: Sequencing chromatograms of persons from the family; the homozygous change C>T in four affected individuals V-7, V-8, V9, and VI-1; the heterozygous change in two unaffected individual V-4 and V-10. Arrows indicate the position of the mutation. B: Sequencing of exon 2 of the EDN3 gene; Highlight shows primer designed for this region

ber is damaging) by SIFT and PolyPhen-2 analysis, respectively.[12] We are reporting second family with four affected persons with same mutation in this position of the *EDN3* gene. Our findings in multiple lines of in silico computational analysis (MutationTaster, CADD, etc.) have been supported the deleterious effect of the variant on the gene or gene product(s). But yet Based on ACMG guidelines, this variant has been classified as a likely pathogenic variant.

This family included four affected persons who have presented WS malformation. Genetic analysis confirmed *EDN3* mutation which is a causing gene in WS4; none of the patents had HD clinical manifestations, the hallmark of WS4, however, with other atypical clinical picture of the disease (deafness, pigment anomalies). And also five heterozygous persons in this family had no each of criteria effect resulting in the disease. The consequence of *EDN3/EDNRB* interaction for accurate development of neural crest-derived melanocytes and enteric neurons is well acknowledged.[13,14] Indeed, the genes connected with WS4 encode proteins that are indispensable components of a signaling cascade that supervises the progression of melanocytes and the enteric nervous system.[18] Pigmentation anomaly, aganglionic megacolon, and cochlear disorder in mouse models with homozygous mutations in the *EDNRB* or *EDN3* genes was reported in previous studies.[15] Heterozygous *EDN3* mutations have been known in patients with HD and homozygous *EDN3* mutations in patients with WS4. In one of the WS4 families heterozygous members for the *EDN3* gene C159F mutation had one or more WS characteristics, but without megacolon. This was contradictory with recessive inheritance of WS and with dominant mode of HD transmission.[11] Differentiation in the chronological arrangement and sites of distinctive subcategory appearance of cells originated from the neural crest could somewhat interpret the variable manifestations associated with *EDN3* and *EDNRB* mutation. Generally, variable penetrance and phenotypic variability are frequent in neurocristopathies.[16, 17] This could be explained by environmental factors, multigenic inheritance, modifier genes or by accidently incidents acting on cell differentiation in early embryogenesis.[18]It is worth mentioning, a heterozygous *EDN3* mutation in a severe case of Waardenburg-Hirschsprung disease confirms the difficulty in predicting the phenotypic manifestations of *EDN3* mutations and complicates genetic counselling.[15] On the other hand, a similar situation in mutations related to *SOX10* was observed. Most of these mutations generate premature stop codons and cause WS4 with or without neurological manifestations. The severity of the phenotype depends on the mutant mRNA's ability of escaping the nonsense mediated mRNA decay (NMD) pathway.[19, 20]

Conclusion

Determination of WS can commonly be missed because of all attributes are not found in every sufferer and clinical variance is conventional, in spite of several affected members of a single family. So, genetic counseling is pivotal for families with multiple members influenced. However, primitive diagnosis of the disease is based on the recognition of the clinical pictures, for the reasons mentioned it is normally confirmed by identification of a mutation in one of the disease-causing genes. Accordingly, its diagnosis has always been a challenging task for practitioners due to its scarcity and nonspecific presentation. Hence, further molecular scrutinizations are compulsory to attain a definite conclusion.

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REVIEW PAPER

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Prospect of Tele-Pharmacists in Pandemic Situations: Bangladesh Perspective

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ABSTRACT

Introduction. Telemedicine and telehealth technologies are especially effective during epidemic outbreaks, when health authorities recommend implementing social distance systems. Currently, coronavirus COVID-19 has affected 210 countries around the world, killed more than 240,000 and infected more than 3.4 million, according to Worldmeter, 03 May, 2020.

Aim. The article reveals scope of pharmacy professionals in telemedicine sector during epidemic outbreaks.

Material and methods. PubMed, ALTAVISTA, Embase, Scopus, the Science Web and the Cochrane Central Register have been carefully searched. The keywords were used to search out extensively followed journals from various publishers such as Elsevier, Springer, Willey Online Library, and Wolters Kluwer.

Results. Home-care is especially important in these situations because hospitals are not seemingly safe during pandemic outbreaks. Also, the chance to get out of the home during the lockdown period is limited. Telephone-based measures improve efficiency by linking appropriate information and feedback. It can also help provide education at distance on various health issues and topics.

Conclusion. In addition to increasing access to healthcare, telemedicine is a fruitful and proactive way to provide a variety of benefits to patients seeking healthcare; diagnose and monitor critical and chronic health conditions; improve healthcare quality and reduce costs.

Keywords. patient compliance, pharmacist's intervention, telehealth

Introduction

Bangladesh's health care services are becoming unusually concentrated in a small fraction of costly critical health-demanding patients. A large part of these complex-patients suffers from multiple chronic diseases and are spending a lot of money. Tele-pharmacy includes patient counselling, medication review and prescription review by a qualified pharmacist for the patients who are located at a far distance from the pharmacy. The most common way to use telemedicine is a responsive model, primarily physician-led with virtual visits stimulated by alerts using interactive services, which facilitates real-time interaction between the patient and provider.[1] It delivers resilience to services and enables pharmacists to work remotely, reducing the need for long journeys and increasing job satisfaction.[2] The rise of pharmacists

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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in epidemic situations has become increasingly popular in developed countries such as the United States, Australia, Canada and the United Kingdom. Along with doctors, pharmacists can serve as frontline healthcare workers during epidemics. The profession is developed and highly praised in both developed and underdeveloped countries. Millions of professional pharmacists worldwide work in various organizations, and according to data from the International Pharmaceutical Federation (FIP), nearly 75% of them work in patient care.[3] Even in the United States, the continued lacking of primary health providers and medical specialists has made it possible for pharmacists to care for ambulatory patients with chronic diseases in a variety of treatment services.[4] This study contributes to the existing literature by describing eligibility of pharmacists in telemedicine for pandemic pharmacy services, which are currently nonexistent in Bangladesh.

Aim

The article reveals scope of pharmacy professionals in telemedicine sector during epidemic outbreaks.

Material and methods

Research conducted a comprehensive month-long literature search, which included technical newsletters, newspapers and many other sources. This study started in February 2020, when the Philippines reported its first death outside China. PubMed, ALTAVISTA, Embase, Scopus, the Science Web and the Cochrane Central Register have been carefully searched. The keywords were used to search out extensively followed journals from various publishers such as Elsevier, Springer, Willey Online Library, and Wolters Kluwer. Medical and technical experts, pharmacy professionals, hospital staffs and journalists have given valuable suggestions. Projections were based on review of tele-pharmacists in both general and pandemic health situations, eligibility of pharmacists in telemedicine in general, present under-utilization scenario of Bangladeshi pharmacists in health services as well as in telemedicine sector. Major infrastructure revolution in both pharmacy education and country's technological advancement are necessary to build an effective telemedicine system in this country.

Present Socio-Economic and Healthcare Situation

Bangladesh is the seventh most populous country in the world and population of the country is expected to be nearly double by 2050, where communicable diseases are a major cause of death and disability.[5,6] A recent Dengue outbreak in 2019, more than 100,000 people was affected in more than 50 districts in Bangladesh in the first 6 months of 2019.[7,8] According to World Bank's Country Environmental Analysis (CEA) 2018 report, air pollution lead to deaths of 46,000 people in yearly in Bangladesh.[9] Although a riverine country, 65% of the population in Bangladesh do not have access to clean water.[10] Both surface water and groundwater sources are contaminated with different contaminants like toxic trace metals, coliforms as well as other organic and inorganic pollutants.[11] Studies in capital Dhaka and Khulna also found that about 80% of fecal sludge from on-site pit latrines is not safely managed.[12] Nearly half of all slum dwellers of the country live in Dhaka division and 35% of Dhaka's population are thought to live in slums.[13,14] A recent research demonstrates widespread poor hygiene and food-handling practices in restaurants and among food vendors.[15] Less than 10% hospitals of this country follow the Medical Waste Management Policies.[16] In 2017, 26 incidents of disease outbreak were investigated by National Rapid Response Team (NRRT) of Institute of Epidemiology, Disease Control and Research (IEDCR).[17] Economic development and academic flourishment do not represent development in health sector. Out of the pocket treatment cost raised nearly 70% in the last decade.[18] Although, officially 80% of population has access to affordable essential drugs, there is plenty of evidence of a scarcity of essential drugs in government healthcare facilities.[19] Surprisingly, the country's pharmaceutical sector is flourishing, exports grew by more than 7% in last 8 months although total export earnings of the country drop to nearly 5%.[20] It has been found in Bangladesh that more than 80% of the population seeks care from untrained or poorly trained village doctors and drug shop retailers.[21] According to WHO, the current doctor-patient ratio in Bangladesh is only 5.26 to 10,000, that places the country at second position from the bottom, among the South Asian countries.[22] According to World Bank data, Bangladesh has 8 hospital beds for every 10,000 people; by way of comparison, the US has 29 while China has 42.[23] Tobacco is responsible for 1 in 5 deaths in Bangladesh, according to the WHO, kills more than 161,000 people on average every year. Around 85% population of age group 25-65 never checks for diabetes.[24] Joint survey of the Power and Participation Research Centre and BRAC Institute of Governance and Development (PPRC-BIGD Rapid Response Survey) reveals that per capita daily income of urban slum and rural poor by drops by 80%, due to present countrywide shutdown enforced by the government to halt the spread of Covid-19. 40% to 50% of these population took loans to meet the daily expenses.[25]

Pharmacy Education in Bangladesh

In many developing countries, including Bangladesh, pharmacy education is still limited to didactic learning which produces theoretically 'skilled' graduate professionals. Bangladesh's pharmacy curriculum doesn't really meet the minimum requirement for adequate

clinical, hospital and community pharmacy education, as it is still linked to an old pharmacy model e.g. based on chemistry and basic sciences. That is present curriculum produces Pharmacist only to work in the pharmaceutical industry and jobs in this field of work is going to be saturated. No university so far have modified their curriculum including topics as epidemiology, pharmaco-economics, clinical medicines, community skills. Manpower development for community pharmacies in Bangladesh is not systematically regulated and constitute an important public health issue. Three levels of pharmacy education are currently offered in Bangladesh leading to either a university degree, a diploma or a certificate. Graduates with degrees work in industry while those with diplomas work in hospitals.[26] Pharmacy is taught in about 100 public and private universities in Bangladesh and about 8000 pharmacy students graduate every year.[27] Due to a lack of government policy, hospital, community, and clinical pharmacy in Bangladesh were not well developed.[28] In real Bangladesh pharmacy practice areas for graduate pharmacists in industry i.e. industrial pharmacy practices, in marketing or regulatory sections are limited. The educational system of pharmacy is one of the major reasons for bounded pharmacy practices because the courses included in bachelor degree principally emphasize on industrial practices.[29] Over 90% of B. Pharm curriculum emphasizes on product-oriented knowledge whereas only around 5% of the total course credits are allocated toward clinical pharmacy. This curricular framework indicates a minimum emphasis on patient care education.[30] However, the graduates who pass out do not get employment easily due to their inadequate training, lack of thorough knowledge of fundamental concepts and practical skills.[17] Accordingly, qualified graduates leave for overseas where they are offered more prosperous jobs. Researchers argued that pharmacy education in Bangladesh can contribute to public and private benefits if its process determines a realistic pattern.[31]. This system could be more beneficial to the public if the excellent hospital and community practices are introduced properly and also by involving the pharma professionals e.g. pharmacists and other skilled health care providers.

Present State of Pandemic Situation Handling by Bangladeshi Hospitals

More than 70% of the 9455 coronavirus cases detected in Bangladesh (as on 03, May, 2020) have been reported in Dhaka division and half of them are in capital Dhaka.[32] The virus hit a total of 11 out of the 64 districts in the country until 05.04.2020 after the first known cases were reported around a month ago, according to the government's disease control agency IEDCR.[33] Amidst this global crisis, Bangladesh has been identified as one of the 25 most vulnerable countries to be affected by the fast-spreading virus. From 1st April to 14th (IEDCR update until 19.04.2020 is shown in figure 1), Covid-19 cases became 20-fold and by 30.04. 2020, it was confirmed in 63 out of 64 districts, taking the officially Covid-19 death toll to 168.[34,35] Many patients with fever, cold and breathing problems – which are also COVID-19 symptoms – have gone untreated as the hospitals in Dhaka are sending them to the IEDCR for coronavirus test.[36] Many doctors are not providing services fearing the contagion and lab technicians are shunning workplaces halting medical tests, according to the patients. In some cases, serious patients who are not affected by COVID-19, moved from one hospital to the other but could not receive treatment and finally died, the media reported. In another case, the doctor fled leaving the patient behind.[37-40] Doctors and other healthcare workers say they do not have adequate personal protective equipment and the health system cannot cope with the outbreak.[41] Police have locked down a total 52 areas of Dhaka after Covid-19 positive patients were found in the localities.[42] Experts say elderly people infected with coronavirus need ICU support the most. The number of older persons in the country is over 0.8 million.[43] In reality, hospitals in Bangladesh have less than 1200 ICU beds (432 govt, 737 private) in total against a population of 161.4 million people.[44] The health minister on 29.03.2020 reported that there are only 500 ventilators in the country.[45]

Underutilization of Hospital Pharmacy

Compared with developed countries, the pharmacy profession is still lagging behind in developing countries in a way that the pharmacy professionals have never been seen as part of the health care team either by the community or by the health care providers. Though hospital pharmacists are recognized in many developed nations for their importance as a healthcare professional, in most developing countries it is still underutilized or underestimated.[45-48] Hospital pharmacy practice has just begun in some modern private hospitals in Bangladesh, which are inaccessible to most people because of the high cost of these hospitals to patients.[49] People are totally unknown to the responsibilities of hospital pharmacist, even they don't seek for recruit for hospital pharmacist in any hospital except a few aristocrat hospitals.[50] A Dhaka survey found nearly 50% of the respondents with acute respiratory disease (ARI) symptoms identified local pharmacies as their first point of care. Licenses are provided by the Directorate-General of Drug Administration to drug sellers when they have completed a grade C pharmacy degree (i.e. 3 month course) for the legal dispensation of drugs but a grade A pharmacy degree holder, having a B. Pharm or Pharm. D degree should be more equipped to handle these situations, if trained properly. Pharmacist's knowledge and help-

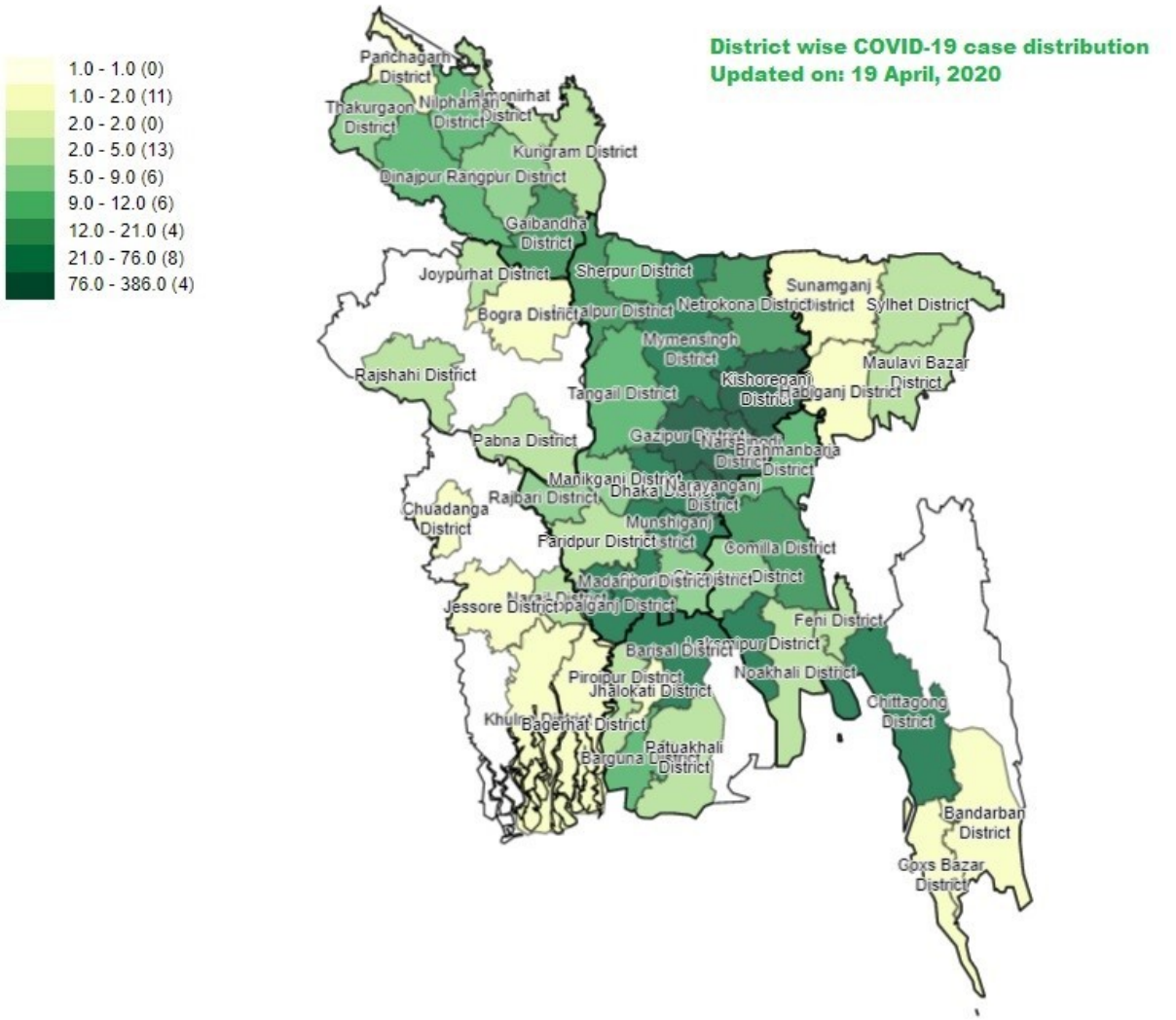

Fig. 1. The Mapping of COVID-19 Confirmed Cases in BANGLADESH, 19 April 2020 (Source: IEDCR Web)

fulness were identified as two key determinants which could not only satisfy and promote willingness to pay for the service.[51,52] They can individualize the medications and their dosing according to the needs of the patient, which can minimize the cost of care for the medication. In Bangladesh, however, graduate pharmacists do not engage directly in-patient care. Here, pharmacies in hospitals are primarily run by non-clinically educated, diploma pharmacists.[28] If the hospital pharmacy is established, patient care, proper dispensing of medications, and other patient-oriented issues can be handled properly. By maintaining a hospital pharmacy quality control program, the health sector can be enriched.

Prospect of Pharmacists in Patient Management Service and Telehealth Care

Pharmacists are the third largest healthcare professional group in the world after physicians and nurses.[53] At present, Hospital Pharmacy has created enormous job opportunities, where graduate pharmacists play a vital role in patient rearing, rehabilitation and wellness. A professional pharmacist at a clinic, hospital and community care can determine what to do in a given disease situation, preventing and counteracting any situation of health danger, ensuring high quality healthcare to seafarers all over the world.[54-56] The country has a huge opportunity to recruit these pharmacists at Telehealth Care. In each call, a pharmacist can provide both appropriate and quality information from the most recent medical systems. Studies show that the lack of proper medication management leads to higher healthcare costs, longer hospital stays, morbidity and mortality. Further, it was reported that one in every five hospitalizations was related to post-discharge complications and about seventy percent were related to proper use of the drug. In 2017, the World Health Organization committed to minimizing serious, avoidable drug-related harm over the next 5 years. Pharmacists' interventions to prevent drug-related problems at three community

hospitals in California saved approximately 0.8 million USD in a year.[57] The estimated annual cost of medication error-based illnesses and deaths worldwide was USD 500 billion due to non-compliance with the clinical intervention and quantities in 2016. Also, the authors estimate that more than 275,000 people die every year for the same reasons.[58] A pharmacist can use simple and non-medical terminology to set the goal for patients to understand the information as well as to fulfill the prescription by proper request. With chronic conditions such as cardiovascular and respiratory diseases, there is ample evidence of the effectiveness of the tele-pharmacist for remote monitoring, communication and consultation.[59] In addition, psychotherapy can also be operated through telehealth as part of behavioral health.[60] The pharmacy-related needs of pandemic patients have similarities with the traditional patient population, but with different emphasis.[61] For example, when providing consulting services to patients, instead of focusing on medications as usual, their queries relate primarily to the knowledge of medical prevention and basic details on COVID-19, such as mask selection and standard COVID-19 signs and symptoms, symptomatic treatment options, breathing difficulties or cough management in comorbid situations, reinforcing behaviors that limit the spread of the pandemic, including social distancing and remaining in the home whenever possible through phone calls/video conferencing.[62,63] Earlier, Student pharmacists served as an effective education resource for patients regarding the H1N1 pandemic.[64] Sorwar et al, 2016 revealed that the existing telemedicine service reduced cost and travel time on average by 56% and 94% respectively compared to its counterpart conventional approach with high consumer satisfaction.[65]

History of Telehealth Service in Bangladesh

The year 1998 represents a milestone for eHealth in Bangladesh when the first eHealth project was introduced by Swinfen Charitable, a non-profit institution. It associated collaborative work between the Center for Paralyzed Rehabilitation (CRP) in Bangladesh and Haslar Royal Navy Hospital in the UK. In the same year the Ministry of Health and Family Welfare (MoHFW) launched its first initiative on eHealth.[66,67] Just a year afterward the private enterprise Telemedicine Reference Center Limited (TRCL) started providing healthcare with mobile phones. The Bangladesh Telemedicine Association (BTA), a professional coalition, was created in 2001. That has provided a platform for ongoing and sparse eHealth initiatives in the country. A similar platform, called the Sustainable Development Network Program (SDNP), was formed in 2003 with the aim of establishing better cooperation and understanding between providers.[68] Later in 2006, TRCL paired with GrameenPhone (GP) and established the Health Line:789 subscriber mobile help desk.[69,70] A number of NGOs subsequently developed an interest in eHealth and mHealth, including BRAC, the Sajida Foundation and DNet.[71] In addition, Bangladesh launched a toll-free national emergency aid line 999 in December 2017 to meet immediate needs in the event of any accident, crime, fire or ambulance.[72] In addition, the IEDCR has launched 17 hotline numbers for the said Covid-19 outbreak.[73]

Challenges of Tele-pharmacy Implementation

Firstly, it has limited evidence of its effectiveness beyond that of intervention by a traditional pharmacist. This favors the skepticism of both physicians and patients towards these services and limits their acceptance in the community.[74] Second, the tele-pharmacy is a service based on the technology. Thus, the driver is technology but also the limiting factor for its implementation. Establishing a tele-pharmacy service involves not only meeting technological requirements but also a considerable amount of time, effort and money.[75] Third, effective tele-pharmacy services should be based on standardized healthcare delivery models, and require appropriate regulations that may differ from country to country. For example, such facilities are not permitted or even restricted in some countries, while adequate legislation is available in others such as USA, Italy and other European countries.[76-79] Unfortunately, despite the rampant potential of tele-pharmacy in many countries, the laws and policies governing pharmacy operations do not adequately address the growing sector. Fourthly, the reluctance or inability to use advanced technologies can limit the implementation of tele-pharmacy services from the perspective of both pharmacists and patients, especially in the context of the elderly.[80-85] Fifthly, since tele-pharmacy involves the gathering, transmission and replacement of personal and health information on the web, information security and privacy are major issues. Data sharing of information collected via tele-pharmacy services with other healthcare professionals increases the possibility of security breaches. The security and integrity of patient data is therefore of paramount importance when determining the setup of a tele-pharmacy system of information technology.[86-91] Sixth, the integration of tele-pharmacy services in the national healthcare systems and the connection of tele-pharmacy services (including a combination of electronic data entry, prescription order verification, online benefit adjudication, medication dispensing) among different areas of a country requires harmonizing the healthcare systems and related governing laws and setting up proper rules and regulations.[92-94] Seventh, tele-pharmacy services are not yet reimbursed: individuals are required to pay for these services, and the expenses are not covered by pri-

vate or public health insurance.[95-99] This restricts the use of these services by patients who may eventually need them.

Overcoming Challenges

In Bangladesh a number of telemedicine systems were introduced. Telemedicine laws and reimbursement policies since telemedicine practice is increasing on a daily basis in Bangladesh, so structured laws and regulations on doctors, patient issues, licensing of physicians and telemedicine providers are very much needed. Clear rules should be in place on questions of reimbursement. Bangladesh Television (BTV) and other satellite channels can play an important part in popularizing telemedicine. They should broadcast successful cases considering telemedicine's efficacy and cost-efficiency. Telemedicine systems and services compatibility of hardware and software require users to have compatible hardware at both ends of the communications link, which reduces interoperability and the benefits of access to different sources of telemedicine expertise. If the equipment is difficult to access or are less likely to involve practitioners. Equipment for wireless telemedicine is preferable to wire devices. Telemedicine privacy and confidentiality involves the electronic transmission of patient medical records and information from one location to another via the Internet, or other computerized media. Medical information is often delicate, confidential and private. Telemedicine, thus presents significant challenges for safeguarding the privacy and confidentiality of information about patient health. Specific privacy regulations should govern the practice of telemedicine so that patients can feel safe in knowing that confidentiality of their personal information will have to suffer certain penalties.

Conclusion

Overburdened by patient loads and the explosion of new drugs, physicians have increasingly turned to pharmacists for information about drugs, particularly within institutional settings. They acquire medical and medicinal history, check medication errors including prescription, dispensing and administration errors, identify drug interactions, monitor ADR, suggest dosage regimen individualization, provide patient counseling, etc. Among chronic disease patients, particularly those under quarantine, there is a greater challenge in the supply of drugs and compliance with medications, although the safety and effectiveness of care is still critical for these patients. Stronger data on the effectiveness of this area of pharmacy care, together with a critical assessment of its limitations, can raise awareness among the actors involved about its potential and could contribute to a wider dissemination of tele-pharmacy services in public interest. At the end, it can be said that pharmacists can play a role in both medical aids and regulation. But their social acceptance as a frontline patient care provider is necessary first. Similarly, in tele-healthcare, the professional pharmacist can play an essential role that has not been recognized yet due to lack of proper initiatives. We hope that policy makers of Bangladesh are aware of its potential and contribute to the wider promotion of tele-pharmacy services in the interest of the citizenry.

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REVIEW PAPER

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Gastro-esophageal reflux and obstructive sleep apnea – is there a link?

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ABSTRACT

Introduction. The epidemic of obesity has led to an increase in the occurrence of obstructive sleep apnea and gastro-esophageal reflux disease. The mechanism of development of gastro-esophageal reflux disease is multifactorial, and studies conducted in the last decade have shed new light on the causes of its development in patients with sleep apnea and obesity.

Aim. The aim of the study was to discuss the mechanism of development of gastro-esophageal reflux disease is multifactorial, and studies conducted in the last decade have shed new light on the causes of its development in patients with sleep apnea and obesity and the dysfunction of the lower esophageal sphincter.

Material and methods. An analysis of literature regarding gastro-esophageal reflux and obstructive sleep apnea.

Results. In obstructive sleep apnea and obesity, high levels of cytokines and insulin resistance are observed, resulting in disorders in the levels of ghrelin – a hormone responsible for normal gastrointestinal motility.

Conclusion. The effect of deviations in the ghrelin profile on the development of gastro-esophageal reflux disease remains a matter for further research.

Keywords. gastro-esophageal reflux, ghrelin, obesity, obstructive sleep apnea

Introduction

For several decades, an epidemic of obesity has been one of the major health problems in many countries. This results, among other things, in an increase in the occurrence of gastro-esophageal reflux disease (GERD) and obstructive sleep apnea (OSA).[1-3] GERD affects from 8-33% of the population and is defined as a disorder in which the stomach contents flow back up into the esophagus, causing complaints and/or leading to the development of complications.[4] Due to an increasing frequency of the occurrence of GERD-related esophageal adenocarcinoma, an effective prevention of GERD is an increasingly important health problem.[5] GERD most frequently occurs in males and persons with an excessive body weight, whereas inadequate diet, an intensive physical effort, some medicines, and the presence of the esophageal hiatal hernia favour its development.[6] Complaints associated with gastro-esophageal reflux (GER) include a burning sensation in the chest, regurgitation, epigastric pain, empty burping, and discomfort during swallowing.

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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In addition, the stomach contents which flow backwards causing extra-esophageal symptoms, such as hoarseness and chronic cough. GER leads to the development of esophagitis and changes of the type of metaplasia, dysplasia and ultimately esophageal cancer.[4] In order to prevent GER, it is recommended to reduce body weight, discontinue smoking, modify diet, and resign from eating before bedtime. In therapy, prokinetic drugs are used, and drugs that suppress gastric acid secretion, while in the case of the therapy being ineffective, or the presence of complications, surgical treatment is considered.[7]

OSA is the most frequent breathing disorder during sleep, and concerns up to 7-20% of adults.[3] In OSA, there occurs a closure or significant narrowing of the airways while sleeping, resulting in an intensified breathing and waking-up effort. Multiple episodes of apnea cause drops in blood oxygen saturation levels and an increase in sympathetic tone, whereas episodes of waking-up result in sleep fragmentation and decrease in the effectiveness of sleep.[8] It was confirmed that an increase in heart rate and arterial blood pressure, an effect of oxidative stress, and elevation of parameters of the inflammatory state, lead to the development of complications within the cardiovascular system.[9] Clinical symptoms of OSA may be divided into those related with the occurrence of episodes of breathing cessation, pauses in breathing during sleep, snoring and waking-up with the sensation of gasping and, resulting from the lack of effectiveness of sleep, excessive sleepiness in the daytime, chronic fatigue, deterioration of cognitive functions, low mood and morning headaches. The main risk factors of OSA include excessive body weight, male gender, age over 40, large neck circumference and anatomical facial malformations.[10] The diagnosis is made based on the result of polysomnography (PSG), and the degree of severity depends on the value of apnea and hypopnea events (AHI). The strategy of sleep apnea therapy depends on the degree of its severity and concomitant diseases. Apart from the normalization of weight and improvement of sleep hygiene, the use of CPAP therapy is considered as the basic method of treatment which, by maintaining positive airway pressure, prevents collapse of the walls of the throat and maintains patency of the upper airway. In selected cases, preventive treatment brings about good outcomes, consisting mainly in the plasty of the soft palate.[8]

Gastro-esophageal reflux in the course of OSA and in obesity

In OSA, especially in its severe forms, GERD is a serious health problem.[11,12] It remains a matter of debate to what extent GERD is related with OSA, and to what degree it results from common with obesity risk factors.[13-15] The relationship between the two disorders is indicated by a study in which a beneficial effect of the CPAP therapy was confirmed on the course of both nocturnal and daytime GERD by improvement of the function of the lower esophageal sphincter (LES).[16,17] In the past, the occurrence of GER in OSA was explained by drops of pressure in the chest during futile respiratory efforts accompanying apnea. Due to the development of diagnostic techniques and possibilities to perform simultaneously esophageal pH-metry and impedance during PSG, the mechanism of GER has been described among patients with OSA. In their study, Penzel et al. observed the symptoms of GERD in all patients with OSA; however, during simultaneous performance of PSG and esophageal pH-metry, no time relationship was found between the occurrence of the episodes of apnea and esophageal pH drops.[18] Kuribayashi et al. also observed a more frequent occurrence of GER in the group of patients with OSA. Due to simultaneous performance of PSG with manometry and pH-metry, it was indicated that in the pathogenesis of nocturnal GER in OSA, the transistent lower espohageal sphincter relaxation (TLESR) plays the major role, and not the accompanying changes in the pressure gradient between the esophagus and the stomach. The researchers found that TLESR occurred more frequently in patients with OSA, and their number correlated with the number of reflux episodes.[19] In their subsequent study, Kuribayashi et al. observed that during the period of apnea episodes, the reflux of the gastric contents into the esophagus was prevented by compensatory tone increase on the level of gastro-esophageal junction and upper esophageal sphincter.[20] In turn, Xiao et al., in the group of patients with OSA, apart from the observation of a more frequent occurrence of acidic GER, observed an impaired cleaning of the esophagus from refluxed gastric contents.[21]

Obesity, especially of the visceral type, is an important risk factor for GERD. It has been confirmed that an excessive amount of visceral fat (VF) better correlated with the occurrence of GERD that the BMI value or body weight.[14,22-24] The mechanism of GER in obesity is complex and results mainly from a decreased tone and increased number of LES relaxations. An elevated intra-abdominal pressure, a high pressure gradient between the stomach and esophagus, and bad eating habits, were considered as less important factors.[25,26] The role of inflammatory parameters remains unclear, the value of which in obesity is elevated and correlates with the intensity of inflammatory changes in the esophagus. In their study, Nam et al. evaluated the relationships between the occurrence of GERD, and values of inflammatory cytokines and adipokines associated with VF. A significant relationship was observed between the amount of VF, leptin level, and occurrence of inflammatory changes in the esophagus. A similar relationship was found for the level of inflammatory cytokines IL-6 and IL-1; however, the consideration of the amount of

VF and leptin level resulted in cytokines no longer being significant as independent factors related with GERD.[27] Tseng et al., in their study, confirmed morning levels of peptide YY (PYY), ghrelin, leptin and adiponectin between patients with GERD and a control group. In the group of patients with GERD, the morning PYY levels were lower, while the levels of ghrelin slightly higher; however, the observed differences were statistically insignificant.[28]

Obesity is the most important factor for the development of GERD, whereas OSA increases its severity and frequency of occurrence.[15] In both disorders, GERD is the result of LES dysfunction; however, the cause of this dysfunction remains unknown.[19,25] The disorder common for OSA and obesity is an increase in the level of proinflammatory cytokines.[29,30] The concentrations of leptin, motilin, obestatin, adiponectin and resistin are related with the amount of adipose tissue in the body; nevertheless, no significant effect of OSA on their values has been observed.[31-33] Both OSA and obesity exert an effect on the levels of ghrelin.[34] Ghrelin stimulates intestinal motility and accelerates gastric emptying; therefore, its deficiency may result in a prolonged retention of the gastric contents favouring the development of GER.

Ghrelin is a hormone produced mainly within the gastrointestinal tract which, together with obestatin, is produced from preproghrelin- a precursor encoded by the GHRL gene. After disconnection from the precursor, ghrelin- by means of ghrelin O- acetylotransferase- is subject to modification to an acylated form, considered as biologically active. Apart from the acylated form of ghrelin, a des-acylated form of ghrelin is distinguished, the role of which in the body is unknown.[35-37] In addition, the results of determinations of the forms of ghrelin using mass spectrophotometry suggest that all the ghrelin in the body is acylated, while the des-acylated form is an artefact formed in the course of the preparation of samples.[38] Ghrelin participates in the regulation of body energy, and through central effects causes an increased appetite, initiates the intake of meals, exerts an effect on the sensation of taste and the reward center.[39-41] It also participates in the regulation of the metabolism of carbohydrates (by exerting an effect on the levels of insulin and increase in insulin sensitivity), regulation of the sleep-wake rhythm.[42-44] It is credited with a beneficial effect on the cardiovascular system and anti-inflammatory effect.[45,46] The peripheral effects of ghrelin include the stimulation of motility of the gastrointestinal system, acceleration of emptying of the stomach and increase in the secretion of hydrochloric acid.[47] The concentrations of ghrelin show daily variability, its secretion into the blood is of a pulse character and is related with the consumption of meals and the sleep-wake rhythm. The highest levels of ghrelin in blood occur approximately 30 minutes before meals, and their values are proportional to the intensity of the feeling of hunger. After the meal, together with an increase in insulin level, the concentration of ghrelin decreases. At night, the level of ghrelin initially increases and remains on a relatively high level, whereas during the second part of the night it gradually decreases, to increase again before the consumption of breakfast.[39,42,43]

Ghrelin profile in the course of sleep disorders and eating disorders

With obesity, decreased ghrelin values in a daily rhythm are observed, also its amplitude and mean levels are lower, except for morning levels which, according to the majority of reports, are higher in individuals with a normal body weight.[39] One of the potential causes is hyperinsulinemia accompanying obesity. This is suggested by the results of a study in which a mealtime increase in the level of insulin, similar to administration of exogenous insulin, resulted in a decrease in the ghrelin level.[44] In turn, while losing weight, the reduction of calories in the diet is associated with an increase in the ghrelin levels, up to very high values observed in the course of anorexia nervosa.[39,48] The subsequent disorder potentially decreasing ghrelin values is an increase in the levels of inflammatory parameters observed in obesity. Ghrelin is considered as a factor inhibiting inflammatory state, in addition, decreased ghrelin levels accompany an elevation of inflammatory parameters in the course of rheumatoid arthritis and in the case of Takayasu's arteritis.[49,50] The lack of effective sleep is the subsequent factor related with disorders in the ghrelin level. The result of studies assessing the effect of sleep deprivation and OSA on the level of ghrelin vary; in the majority of observations an elevated fasting level of ghrelin is noteworthy, as well as its lower values during the first hours of sleep.[33,43,45,51] In their study, Spiegel et al. evaluated the effect of short-term sleep deprivation on diurnal levels of ghrelin and leptin in a group of healthy individuals. During the period when the study participants experienced sleep deprivation, higher diurnal ghrelin levels and lower leptin levels were observed, and these changes were accompanied by a greater feeling of hunger and an increased appetite.[52] In turn, Dzaja et al., in their study of persons subjected to sleep deprivation, did not observe any increase in ghrelin levels during the first hours of the night, while no differences in ghrelin values were observed during the day.[42] Motivala et al. in a conducted study found that nocturnal ghrelin values were lower in a group of patients with chronic insomnia, compared to the control group.[53] In their study, Takahashi et al. evaluated morning levels of acylated and des-acylated ghrelin in patients with OSA, and the effect of treatment using the CPAP therapy. In the group of patients with OSA, ghrelin values were higher, while a repeated assessment after one-month CPAP therapy showed a de-

crease in the level of acylated form of ghrelin, compared to the values observed in the control group.[54] Nevertheless, in a study by Weiying et al., in a group of patients with OSA, morning ghrelin levels were lower than those observed in the control group.[34] In turn, Papaioannou et al. examined patients with OSA and did not observe any deviations in the determinations of fasting ghrelin, and those performed at 22.30.[55] Similarly, in the study by Sanchez-de-la-Torre et al. conducted among patients with OSA, no differences were found in the daily ghrelin profile, compared to the control group.[32] Fluctuation in ghrelin levels, similar to obesity, may be secondary with respect to elevated levels of inflammatory parameters and insulin resistance, accompanying sleep deprivation and OSA.[30,51] Higher fasting ghrelin levels are associated with a stronger feeling of hunger; therefore, they may be responsible for the tendency towards consumption of a higher amount of calories observed among persons with sleep disorders.[52] Unfortunately, in patients with OSA, this mechanism, by increasing the calorific value of diet, may lead to an increase in body weight and further intensification of breathing problems during sleep.

Occurrence of GERD and ghrelin

The mechanism of the development of GERD is multifactorial. Observations carried out by Nataha et al. conducted on rats indicate the role of ghrelin in the occurrence of gastrointestinal motility disorders accompanying GERD.[56] Ghrelin stimulates intestinal peristalsis and accelerates the emptying of the stomach; therefore, its low values, through prolonged gastric emptying may play a role in the development of GERD.[57] This hypothesis has been supported by Agrawal et al., who after administration to three groups of patients subsequently ghrelin, capromorelin/ghrelin receptor agonist, and placebo, observed in the first two groups a significant reduction in the number of reflux episodes.[58] Similarly, in a study by Rubenstein et al, lower fasting ghrelin levels correlated with the occurrence of GERD.[59] In turn, in the previously mentioned study by Tseng et al. conducted in patients with GERD, morning ghrelin levels were higher than in the control group; however, this difference was statistically insignificant.[28] In a study by Eren et al. no relationship was found between fasting ghrelin values and the intensity of GERD.[60] The available studies do not consider the pulsating character of ghrelin secretion; therefore, an assessment in a daily profile would allow full determination of its importance for the development of GERD.

Conclusion

GERD is an important health problem among patients with OSA and obesity. In both disorders, LES dysfunction plays the major role in the pathogenesis of GERD. Ghrelin is responsible for gastric emptying; therefore, its low values may favour the development of GER. A decrease in nocturnal ghrelin levels observed in sleep deprivation and OSA, and in the case of obesity in the whole daily profile, may be responsible for a different course of GERD. For this reason, further studies and evaluation the role of ghrelin in the pathogenesis of GERD are recommended, especially in the context of LES function and esophageal motility.

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CASUISTIC PAPER

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Traumatic "TERSON SYNDROME PLUS": Pneumocephalocele with optic atrophy

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ABSTRACT

Introduction. Terson Syndrome is subarachnoid hemorrhage (SAH) with sub retinal hemorrhage flowing through channel. Reduced vision in such fresh case is due to hemorrhage itself, blocking macula/other photo receptors in the long run macular cellophane retinopathy which causes profound visual loss. SAH causes neurological problems which can become a risk factor for evacuating blood from vitreous. Hypertension is commonest cause to cause Terson Syndrome, but trauma is also devastating cause as it can lead to irreversible visual consequences like total loss of perception of light or blindness.

Aim. Here we describe a case of Terson Syndrome plus disease features SAH in frontal lobe.

Description of the case. When there is traumatic pneumocephalocele, it gives space to blood to imbibe towards bony optic canal and form hematoma around nerve sheath which causes compression around the same and leads to optic atrophy. Optic nerve can be injured by direct traumatic dissection during road traffic accidents (RTA), but even without that blood may accumulate around optic nerve and in turn leads to formation of hematoma and subsequently pressure induced optic atrophy. Moreover, blood can slowly travel to sub hyaloid space/sub retinal space (beneath internal limiting membrane or sub ILM) with probable gliosis covering typical boat shaped blood as seen in this case. This sub ILM hemorrhage or gliosis may have resolved through three injections of Triamcinolone in the orbital floor (OFTA) near apex, but optic atrophy snatches vision. This protocol was followed to treat traumatic compressive (peri optic hematoma) optic neuropathy and traumatic retinopathy associated with sub hyaloid hemorrhage.

Conclusion. Diagnosis of Terson syndrome plus disease was established by addressing all features on computed tomography (CT) scan and magnetic resonance imaging (MRI). Plus, features include pneumocephalus, optic nerve sheath hematoma, optic atrophy and gliosis over sub-hyaloid hemorrhage, typical boat shaped. The part of hemorrhage still endured as seen on optical coherence topography, but vision was lost by virtue of optic atrophy. OCT shows clot in sub hyaloid space.

Keywords. optic atrophy, sub retinal, subarachnoid hemorrhage, sub hyaloid, Terson syndrome plus

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Introduction

First described by Litten in 1881 and then in 1900 by French ophthalmologist Albert Terson.[1,2] Terson syndrome is now recognized as intraocular haemorrhage associated with subarachnoid haemorrhage (SAH), intra-cerebral haemorrhage, or traumatic brain injury.[1] Haemorrhage may be present in the vitreous, sub hyaloid, or intraretinal/sub-internal limiting membrane.

Several possible pathophysiologic mechanisms for Terson syndrome are known. Blood present in subarachnoid may be directly transmitted forward through the optic nerve sheath.[1,3] More commonly, a sudden increase in intracranial pressure leads to rapid effusion of CSF into the optic nerve sheath which causes dilatation of the retro bulbar optic nerve mechanically compressing central retinal vein and ensuing venous hypertension results in rupture of thin retinal vessels. This mechanism is consistent with the fact that Terson syndrome can be seen in patients without intracranial haemorrhage.[4]

Aim

Here we describe a case of Terson Syndrome plus disease features SAH in frontal lobe.

Description of the case

A 38-year-old male came to our hospital with history of road traffic accident (RTA) 4 months back, he sustained head injury and was treated outside for brachial plexopathy. After recovering from head injury components, the patient presented with total loss of vision in left eye. On examination his best corrected visual acuity (BCVA) was 6/6 in right eye and no perception of light (PL negative) in left eye. Anterior segment was within normal limits. Relative afferent papillary defect (RAPD) was present in left eye. Fundus examination showed white boat shaped dirty white sub hyaloid lesion involving macula with disc pallor (Figure 1).

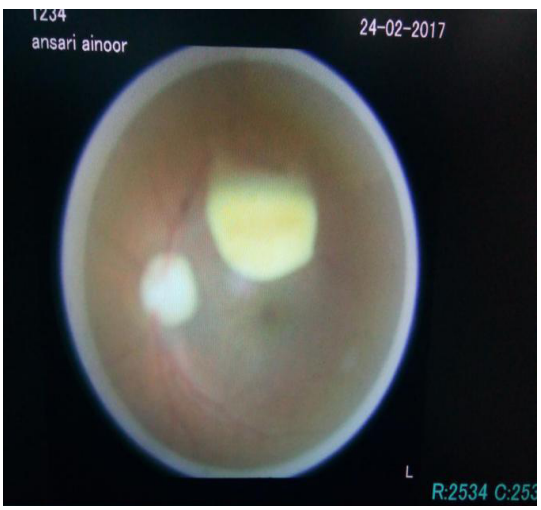

Fig. 1. Initial presentation showing optic atrophy with peri macular gliosis

Extra ocular movements were free and full in both eyes. Initial computed tomography (CT) of head showed contusion involving left frontal region with perilesional edema with subarachnoid haemorrhage in basal cisterna (Figure 2). MRI brain showed normal study except thickening of optic nerve in left side and haemorrhage around optic nerve (Figure 3).

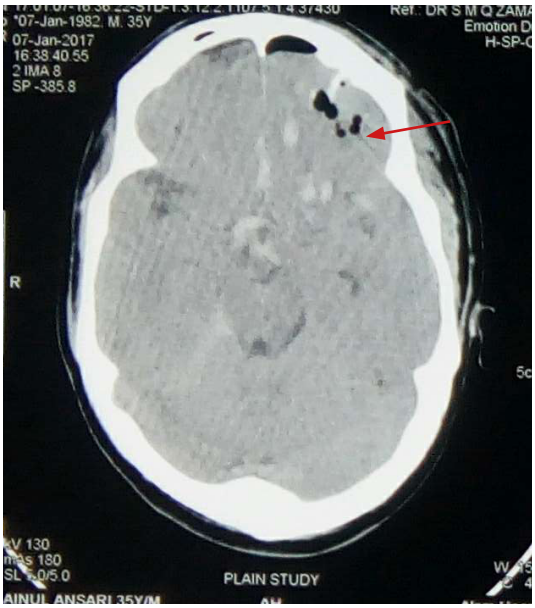

Fig. 2. CT scan of brain showing subarachnoid haemorrhage and pneumocephalus in frontal lobe – black arrow shows subarachnoid haemorrhage, blue arrow shows pneumocephalus in frontal lobe

Presence of RAPD with MRI-proven perineural haematoma confirmed traumatic optic neuropathy. Moreover, sub hyaloid gliosis over macular area was the indication for OFTA. Three injections on monthly interval have resolved gliosis exposing a faded sub hyloid haemorrhage (Figure 4). OCT findings ruled out sub ILM haemorrhage (Figure 5). On subsequent follow up fundus photography, the haemorrhage resolved but the patient's visual acuity did not improve

Key points of the case:

1. Frontal lobe haemorrhage leading to haematoma near optic nerve
2. Retinal Haemorrhage with gliosis
3. Gliosis resolved with periocular steroid
4. No mortality even with SAH and Terson syndrome
5. Optic nerve atrophy due to pressure of optic nerve haematoma leading to high ocular morbidity

Discussion

When vitreous hemorrhage occurs in association with subarachnoid hemorrhage is known as Terson syndrome. Intraocular hemorrhages of any type, call it retinal, sub hyaloid, or vitreous all of these have been documented in 10–40% of individuals with subarach-

noid hemorrhage. It can also occur in association with intracranial hemorrhage and elevated intracranial pressure. Diagnosis of Terson syndrome is clinically important, as it is associated with significantly higher mortality. Up to 77% of these cases are overlooked on daily reports. Timely ophthalmologic intervention to prevent long term visual loss is of utmost importance.

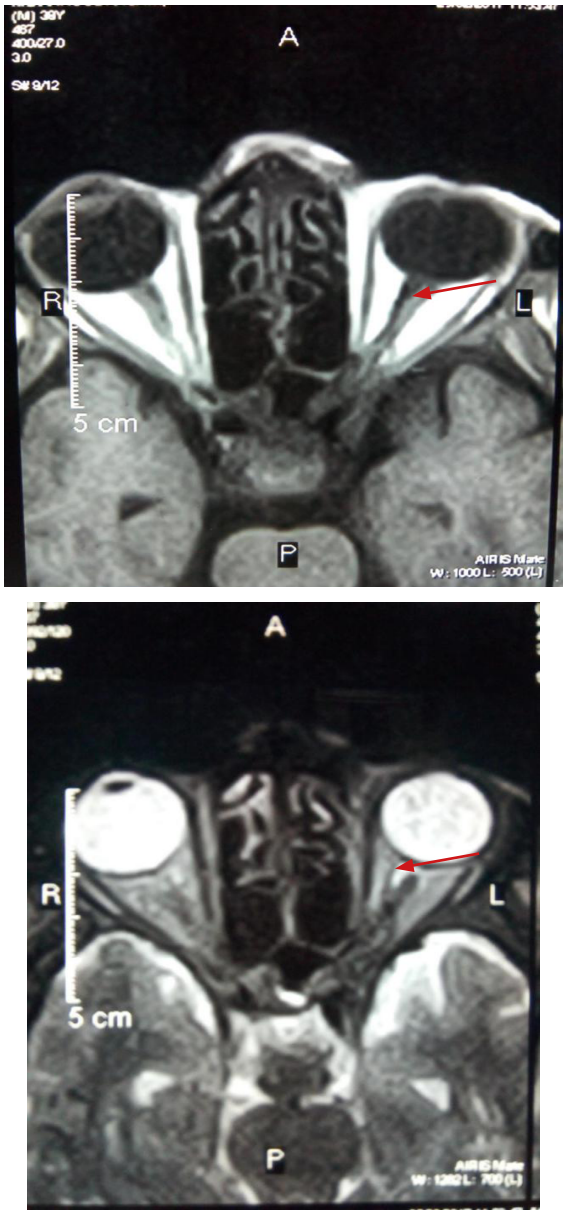

Fig. 3. T1 and T2 weighted images showing hematoma near optic nerve in left eye (blue and black arrows)

Fluorescein angiography has demonstrated a leakage site at the disc margin in a patient with Terson syndrome with vitreous haemorrhage. This theorizes potential damage to the peripapillary retina induced by increased intracranial pressure transmitted through the optic nerve sheath.[4]

Terson syndrome can present with dome-shaped haemorrhages in the macula.[5] A macular "double ring" sign may be seen with the inner ring caused sub-ILM haemorrhage and the outer ring caused by sub-hyaloid haemorrhage.[6]

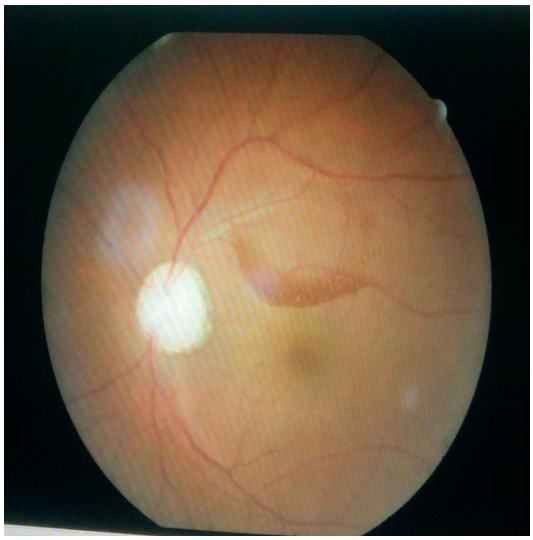

Fig. 4. Treatment with peri ocular steroid resulting in disappearance of gliosis exposing retinal haemorrhage

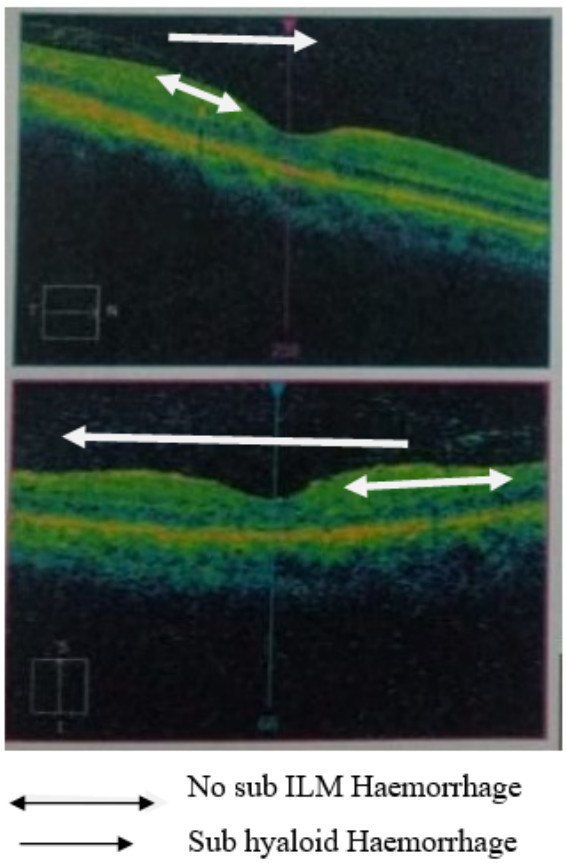

Fig. 5. OCT image showing sub hyaloid haemorrhage

Even if intraocular haemorrhages most frequently develop in the first hour after SAH, Terson syndrome can have a delayed onset, with reports of intraocular haemorrhage occurring up to 47 days after SAH.[1,7,8]

Low Glasgow coma scale, high Hunt and Hesse grade, and high Fisher grade are associated with a higher incidence of Terson syndrome.[1]

Neurological outcomes and mortality rate are worse in patients with SAH and Terson syndrome than patients with SAH alone.[1] In a study by Pfausler, mortality was 90% in patients with SAH and Terson syndrome and 10% in those with SAH without Terson syndrome.[9-11]

Swallow investigated the use of orbital CT to identify intraocular haemorrhage in patients with Terson syndrome. There was presence of retinal crescentic hyper densities and retinal nodularity in CT in two-thirds of patients with Terson syndrome.[12-14] Thus CT may be useful to identify possible Terson syndrome prior to an eye exam.

Multiple complications have been reported after Terson syndrome. Epiretinal membrane is the most common sequel of Terson syndrome, with an incidence of 15-78%.[15-18] Vitreous blood may cause ERMs by inducing glial proliferation and disruption of the ILM.[19]

In 20% of patients with Terson syndrome retinal folds/perimacular folds occur. Also, occurrence of retinal detachment in 9% and ghost cell glaucoma in around 4% cases has been seen reported.[19] Proliferative vitreoretinopathy and preretinal fibrosis have also been reported after Terson syndrome.

Studies have shown no significant difference in final visual acuity between patients who were conservatively managed and those who underwent PPV. However, visual recovery was more rapid in the vitrectomy group despite these patients having denser vitreous haemorrhage.[17]

Role of systemic and periocular steroid is the mainstay of to prevent visual loss in neuro ophthalmology cases but use of OFTA proved beneficial in this case.[20] So this approach may be tried as it is very safe, non-oculo-hypertensive and without any systemic side effects.[21] However this needs more studies in future.

Conclusion

Terson Syndrome is a known entity particularly in cases of brain haemorrhage due to hypertensive crisis and haemorrhagic stroke. Traumatic subarachnoid haemorrhage with sub hyaloid/sub retinal haemorrhage is rare. Several possible path physiologic mechanisms for Terson syndrome are well known, but it is always good to assess any disease from different perspective, as minute finding can be vital for new outcome. So the case of "Terson Syndrome plus" a new clinical entity discussed here is having signs of initial sub arachnoid hemorrhage in frontal lobe along with pnemoencephalocele with hematoma in optic canal and sub hyaloid haemorrhage. Essentially Terson syndrome plus is the combination of multiple features, namely Subarachnoid haemorrhage in frontal lobe with pneumoencephalocele, optic canal haematoma sub hyloid/sub retinal haemorrhage and subsequent blindness due to pressure atrophy of optic nerve.

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CASUISTIC PAPER

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Triple thyroglossal duct cysts in an adult: a rare case report and review of literature

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ABSTRACT

Introduction. Thyroglossal duct cyst (TDC) is the most common cause of congenital neck mass. These can present anywhere from foramen caecum to mediastinum. Usually presents as a solitary cyst, the double thyroglossal cyst is very rare and a triple thyroglossal cyst has never been reported.

Aim. Herein, we report an atypical case of triple thyroglossal cyst, at levels of hyoid, thyrohyoid membrane and thyroid isthmus managed surgically without any complication.

Description of the case. We are presenting case of a 48-year-old female who presented to us with the complaint of anterior neck swelling since birth. On work up it was diagnosed as a case of the thyroglossal duct cyst and was intraoperatively found to have 3 distinct cystic swellings connected to a common stalk lying beneath the hyoid. It was successfully treated by modified Sistrunk's procedure. There was no evidence of recurrence on follow up for 6 months. Considering atypical presentations, there are 9 cases reported with the double thyroglossal duct cyst, TDC within the thyroid gland and sublingual TDC. Such presentations make the diagnosis more challenging, leading to improper treatment.

Conclusion. We are presenting this case as there is no case reported in English literature with a triple thyroglossal duct cyst. An awareness that thyroglossal cyst can present as multiple cysts is important for clinician in order to perform correct surgical management and to avoid the most feared complication of recurrence.

Keywords. complication, diagnosis, duct, recurrence, thyroglossal cyst, treatment

Introduction

Thyroglossal Duct Cyst (TDC) is the most common pathology seen in patients presenting with congenital median neck mass.[1] Majority of these occur infra-hyoid (25-65%) in location.[2] The prevalence of thyroglossal duct cyst is around 7% in general population.[3] The most common presentation is anterior neck mass which moves with deglutition and protrusion of tongue, but may also have atypical presentations like lateral neck swelling or laryngeal communication. Mean age of presentation is 17.3 years.[4] Aetiology remains through stimulation of epithelial remains in the thyroglossal

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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duct, which were left in embryonic life, through upper respiratory tract infections.(5) Dermoid, lipoma, branchial cyst, lymphadenopathy and benign thyroid lesions are common differential diagnoses.[1] The Sistrunk's Operation is the procedure of choice for TDCs due to its low rate of recurrence.[5,6]

Aim

Herein, we report an atypical case of triple thyroglossal cyst, at levels of hyoid, thyrohyoid membrane and thyroid isthmus managed surgically without any complication. We feel necessary to bring this rare anomaly which has not yet been reported to the attention of surgeons operating TDCs and hence reporting this case.

Description of the case

A 48-year-old female presented to the outpatient department with swelling in midline of anterior neck since childhood. Swelling was insidious in onset, gradually progressive, not associated with - discharge, fever, pain and difficulty in swallowing. There was no history suggestive of hypothyroidism, hyperthyroidism or compressive symptoms. There were no other systemic comorbidities. On neck examination, there was 4 cm x 3 cm smooth, well-defined swelling in the anterior aspect of neck, situated between mentum and thyroid cartilage, at & below level of hyoid, moving with deglutition and protrusion of tongue with overlying skin normal (Figure 1). No discharging sinus, ulcer or enlarged lymph nodes were seen. Laryngeal endoscopy was normal.

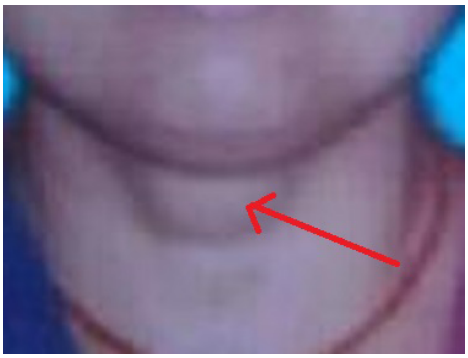

Fig. 1. Neck examination

Ultrasonography neck was performed which revealed a well-defined heteroechoic multiloculated cystic lesion measuring 40x38x25 mm in anterior neck with internal echo. FNAC was done which showed abundant macrophages with thick, mucinous background and ciliated columnar epithelium suggestive of benign cystic lesion. Contrast enhanced computed tomography neck was done which showed a well-defined multi-lobulated thick walled cystic lesion (HU-10) of size 37x29x35 mm in the infra-hyoid region of anterior neck with at-

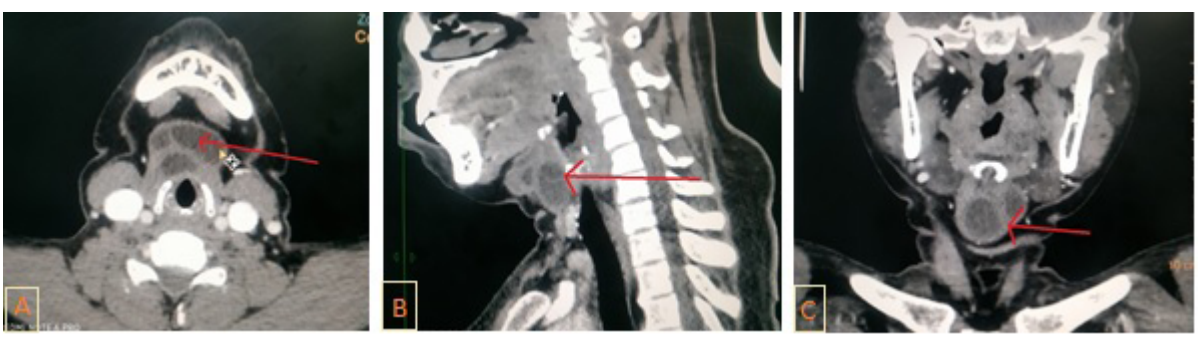

Fig. 2. Contrast enhanced computed tomography of neck

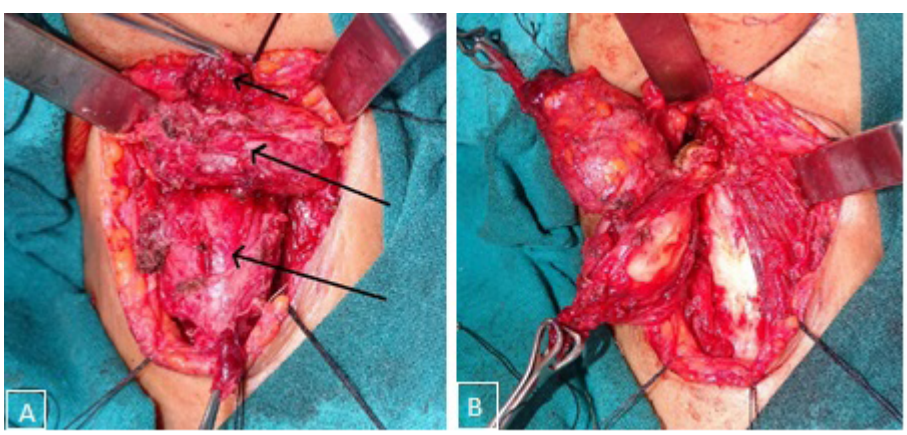

Fig. 3. Three separate cysts during operation

tachment to the isthmus of thyroid gland with few solid components (Figure 2.A, 2.B, 2.C, marked red arrow)

With these findings, the provisional diagnosis of thyroglossal duct cyst was made. Patient was taken up for surgery under general anaesthesia (GA).

Surgery: Sistrunk's operation was done. A transverse incision along the neck crease was given below the inferior border of swelling. Sub-platysmal flap was elevated superiorly till 1 cm above hyoid bone. Strap muscles identified and retracted laterally. Three separate cysts were seen originating from the same tract (Figure 3.A, 3.B)

Inferior most cyst had its attachment to thyroid isthmus. Extracapsular cyst's dissection was done from inferior to superior. A cuff of tissue from thyroid isthmus at its attachment with the inferior most cyst was excised. At the level of hyoid was the superior cyst, the smallest out of three and was excised along with the body of hyoid. Persistent thyroglossal tract was traced superiorly till base of tongue and tied. This was followed by excision of the tract along with all three cysts in Toto. Wound closure was done in two layers. Postoperative period was uneventful. Specimen (figure 4) was sent for histopathology.

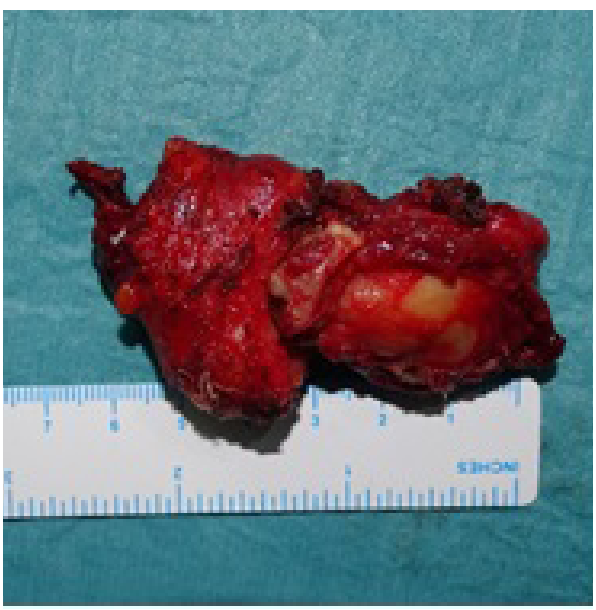

Fig. 4. Specimen obtained during surgery

The postop histopathology report showed oval surface with clear mucinous fluid, outer wall lined by pseudostratified epithelium with follicular cells containing colloid and lined by cuboidal epithelium with intense lymphocytic and macrophage infiltration, corresponding with the diagnosis of thyroglossal duct cyst (Figure 5A, 5B, 5C). Patient was followed up for a period of 6 months and was symptom free with no evidence of recurrence. Figure 6A and 6B shows follow up photo of neck wound at postoperative day 10 and at 6 months.

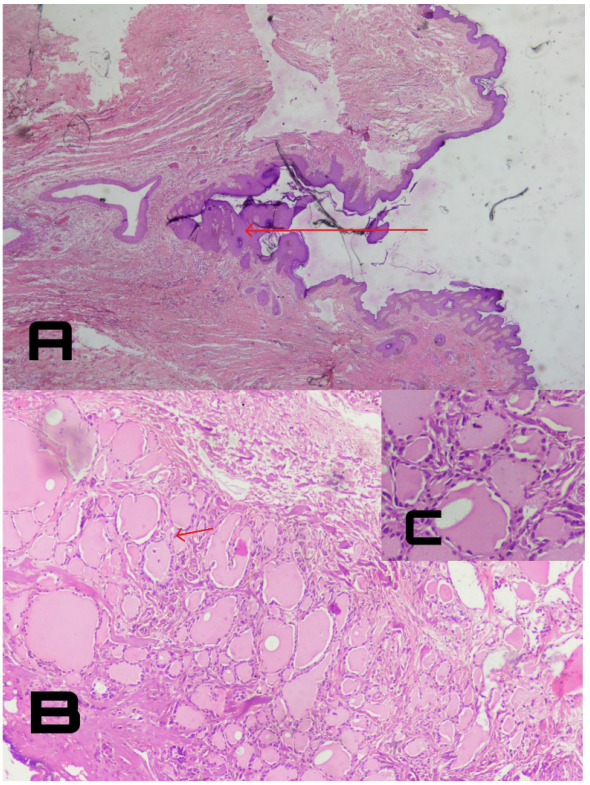

Fig. 5. Thyroglossal duct cyst (H&E stain)

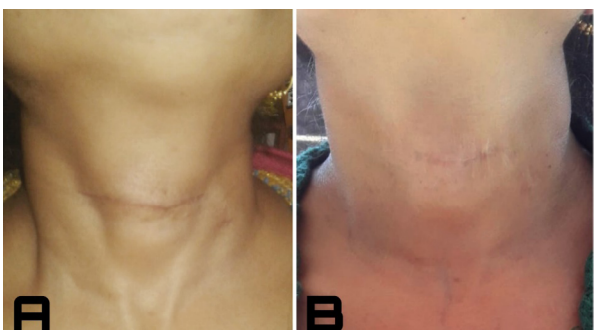

Fig. 6. Photo of neck wound at postoperative day 10 (A) and at 6 months (B)

Discussion

Neck swelling consists of several entities varying from benign (cysts to cyst-like-masses) to malignant. Cystic masses in neck can be either congenital or acquired. TDCs comprise almost 70% of congenital neck cysts.[1] During development, the anlage of thyroid/parathyroid descends in lower neck from the foramen caecum and passes anterior to hyoid, leaving the epithelial tract behind.[1,7] Thyroglossal duct is a transient connection between descending thyroid and pharyngeal endoderm. Foxe 1 gene is responsible for migration of the thyroid bud from tongue base to its normal location.[7] Generally, this tract degenerates in foetal life around 8th week, if persists leads to development of cysts (most commonly), fistulae or solid nodules. These mostly present in paediatric age groups.[3,8] Clinical features vary from asymptomatic to painless cystic swelling in the anteri-

or aspect of neck(most common).[3] Up to one quarter, these cyst present as the draining sinuses. Atypical presentations like swelling not moving with protrusion of tongue, lateral neck swelling, swelling in the floor of mouth, aberrant pharyngeal communication, tuberculous cyst, dysphagia, severe respiratory distress and sudden infant death syndrome may also be seen rarely, making the diagnosis difficult.[3,4,8] Airway obstruction in intra-laryngeal or para-glottic TDC, though a very rare presentation, caused due to mass effect over hypopharynx and posterior displacement of epiglottis, also described as the ball valve effect between laryngeal inlet and cyst.[4,9] It may also mimic a laryngocele.[10] They can be located from tongue to mediastinum anywhere (majority being infra-hyoid in location, 70%) and even within thyroid, very rarely.[8,11]

Diagnosis is mainly clinical, supported by radiology and confirmed on cytology. Ultrasonography (USG) is done to ensure if a normal thyroid gland is present or not. USG shows an anechoic/hypoechoic/hyperechoic midline mass with internal echoes. In USG, there is no significant vascularity with the majority being unilocular and with pseudo solid appearance (Presence of a solid component suggests the possibility of TDC carcinoma or infection).[20,21] Specific features in USG or suspicion of some other pathology warrants use of CT in a case of TDC. Computed tomography characteristics are of low density mass lesion predominantly, with or without septations, and with peripheral rim enhancement rarely (High density lesion correspond to high protein content either due to a malignancy within or infection).[22] The fascial planes of thyroglossal duct cysts are generally well preserved (abnormal fascial planes demonstrate post-inflammatory changes). As in this case, predominantly suspicion of triple TDC was made on CT only. It becomes especially important because as in our case, even multiple thyroglossal cyst may appear as a solitary lesion clinically. Thyroid scintigraphy is done only if ectopic thyroid is suspected. Next step in management comes for FNAC. Cytology will help in characterization of swelling. Pathologic mimics like dermoid, epidermoid cysts, branchial cleft cyst, laryngocele, thymic cysts, lymphatic malformation, ectopic thyroid and necrotic lymph nodes, can be mistaken as TDC.[23] Pathologic features include a respiratory or squamous epithelium lining in the cyst wall, muco-serous glands with inflammatory changes. Primary treatment is surgical excision. Sistrunk's procedure is treatment of choice. From our search, alternate techniques for TDC treatment includes simple cystectomy, Schlange procedure and sclerotherapy (using OK-432 or ethanol). Over a period of time, Sistrunk's operation has been modified than its conventional procedure. Sistrunk's 1920 description of TDC excision defines excision of the ¼ inch of central portion of hyoid along with the cyst and a cuff of soft tissue of same diameter up to and including foramen caecum, followed by repairing the opening in the oral cavity and approximating strap muscles and hyoid. In 1928 description, he no longer advocates dissection in the oral cavity with a success rate of 96%.[6] With time, there have been modifications like (1) coring out the central portion of hyoid using 4.5 mm skin punches and then resecting out under magnification of a 3.5x loupe (2) hyoid cartilage division method.[5,24] Results are seen better including amount the of drainage and operation time, in cases where hyoid was divided at points of non-fusion of the cartilaginous portion of hyoid compared to conventional hyoid bone cutting.[5,6,24] Extended Sistrunk's operation is being advocated for cases where there is a recurrence following Sistrunk's procedure. Regarding TDC excision, there are two surgical approaches (1) cervical approach - Sistrunk's procedure, most commonly used (2) trans-oral endoscopic approach used for lingual or sublingual TDCS. However, there is no data regarding the efficacy of trans-oral approach. Complication of Sistrunk's procedure included local wound infection (most common), seroma formation, hematoma, salivary fistulae, airway stenosis and rarely hypothyroidism.[3] Our literature search shows that Sistrunk's procedure has significantly bought down the recurrence rate. Schlange procedure which is rapid and easier to perform is simple cystectomy with removal of the body of hyoid is associated with around 30 % of recurrence. Sclerotherapy acts by the reduction of lymphatic fluid and shrinkage through the fibrosis but not advocated much due to the presence of another very effective procedure such as Sistrunk's operation and less research regarding its efficacy and outcome. Infection is a common complication seen in patients with TDC due to its anatomical proximity with oral cavity, leading frequent visits to the hospital. Common pathogens include Haemophilus and Staphylococcus. A major problem for management of TDCs is recurrence even in hands of a skilled surgeon, which makes it a challenge for treatment. Maximum recurrence was seen with simple cystectomy and was more common in younger age groups and patient who had a previous history of recurrent infection in TDC, rupture of cyst intraoperatively and skin involvement.[3] Efficacy of postoperative use of drain placement and prophylactic antibiotics is insignificant.[25] Malignant changes in TDCs are rare(-less than 1%) and diagnosed either as incidental finding in postop histopathology(73%) or in preoperative FNAC.[26] Most common of TDCs malignancy were papillary carcinoma followed by squamous variety. Management of TDCs malignancy remains same as original procedure for TDCs (Sistrunk's procedure).

Double TDCs may present as cystic swellings nearby or far away from each other. On literature search,

(using PubMed, Embase, Google scholar, Cochrane review) there are 9 cases reported of double TDCs but none for triple TDC.[11–19] Sarmento et al described a patient with double TDC in floor of mouth on geniohyoid muscles and sublingual region.[16] Yorancilar et al mentioned a double TDC in hyoid and base of tongue.[15] Pueyo et al described a double TDC with one part intrathyroidal and inferred that failure of involution of TDC remains is responsible for cyst development. Yildiz et al in a review mentioned that double TDCs are rare and thyroid scintigrapgy is must in such cases to differentiate it from thyroid pathologies. However, a classical Sistrunk operation suffice as treatment for double TDC. Valentino et al mentioned that ultrasonography is must in cases where suspicion of double TDC is suspected. However, it is not sensitive enough to detect all.

Despite a lot of literature being available on thyroglossal duct cyst, there is limited data on the outcome of atypical presentations of thyroglossal duct cyst. Further research needs to be done regarding the cause of such atypical presentations and their effect on management of disease.

Conclusion

Thyroglossal duct cyst, though a very common entity, may have atypical presentations as double or triple cyst. Failure to identify such variation may lead to inadequate surgery and leaving behind residual disease. Hence, pre-operative radiological as well as intra-operative assessment is important in terms of complete excision and prevention of recurrence.

Compliance with ethical standards

The study has not received funding from any organization or institution and does not involve any potential conflict of interest (financial and non-financial). Procedures performed in the study was in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments.

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CASUISTIC PAPER

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Hyalinising clear cell carcinoma of salivary gland: a case report

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ABSTRACT

Introduction. Clear cell carcinoma, not otherwise specified/hyalinising clear cell carcinoma of the salivary gland (HCCC) is a malignancy that arises in minor salivary glands. It rarely leads to distant metastases or cancer-related death but has the potential for recurrence and focal metastases.

Aim. A case is reported.

Description of the case. A 72 years old female patient has reported to the Clinic of Otolaryngology with a tongue lesion. The patient had no history of malignancy. The lymph node has been surgically removed for further examination. Cords and nests of clear cells and cells with eosinophilic cytoplasm in a hyalinized stroma were identified within the lymph node. After the diagnosis the patient has been transferred to another Oncology Hospital for further treatment.

Conclusion. The diagnosis of clear cell carcinoma may be challenging because many of it's features frequently overlap with other salivary gland lesions.

Keywords. cancer, hyalinising clear cell carcinoma, salivary gland

Introduction

The original description of hyalinizing clear cell carcinoma (HCCC) was published by Milchgrub et al. in 1994.[1-3] HCCC shows a female predominance.[4] The majority of cases occurre in the oral cavity, most commonly the tongue and hard palate. Less common locations include the parotid gland, lacrimal gland, nasopharynx and hypopharynx.[5]

Aim

A case of hyalinizing clear cell carcinoma is reported.

Description of the case

A 72 years old female patient has reported to the Clinic of Otolaryngology with a tongue lesion. Upon examination by the admiting doctor a tumor of the base of the tongue has been identified and a surgical biopsy has

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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been performed. The examination also revealed an enlarged lymph node in the submandibular region, posterior to the submandibular gland.

Our Department of Pathology recieved two 5 mm fragments of the tongue tumor. When examined under the microscope tissue sample consisted of nests of cells with little nuclear atypia and clear cytoplasm alongside abundant chronic inflamation (Figure 1). Immunohistochemical stains revealed these tumor cells to be positive for CK 5/6, CK7 (Figure 2), CK19, and focaly positive for RCC marker. Stains for CK20 and S-100 Protein were negative. Even though network of small, thin walled, „chicken wire" vasculature has not been identified a Renal Cell Carcinoma metastases where taken under consideration.

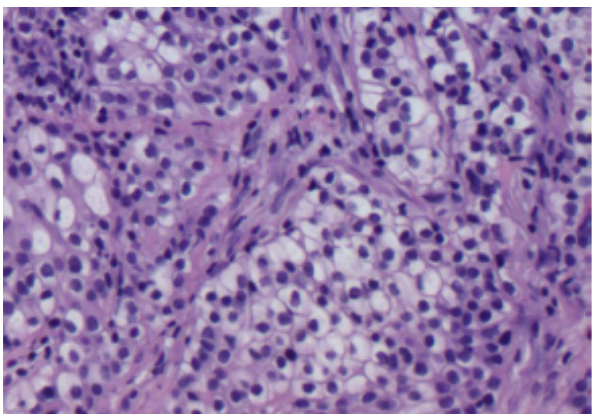

Fig. 1. Nest of neoplastic cells with little nuclear atypia and clear cytoplasm (200x, H&E stain)

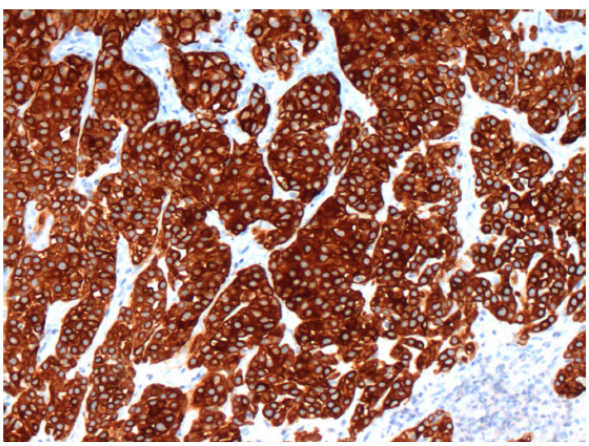

Fig. 2. Positive stain for CK7 (200x)

Renal cell carcinoma (RCC) is a kidney cancer that originates from the cells that line the proximal convoluted tubule.[6-28] It accounts for about 2–3% of all malignant tumors.[7-10] Most cases are diagnosed in the 7th decade of life.[8] Metastases to the head and neck region account for 3.3% of cases.[9-22] They may occur many years after surgical treatment of the primary tumor. [10-34]

The patient had no history of malignancy. She underwent an abdominal CT scan wich excluded kidney tumors. At the same time a fine needle aspiration (FNA) has been performed on the enlarged lymph node but the cytological examination was nondiagnostic.[35,36]

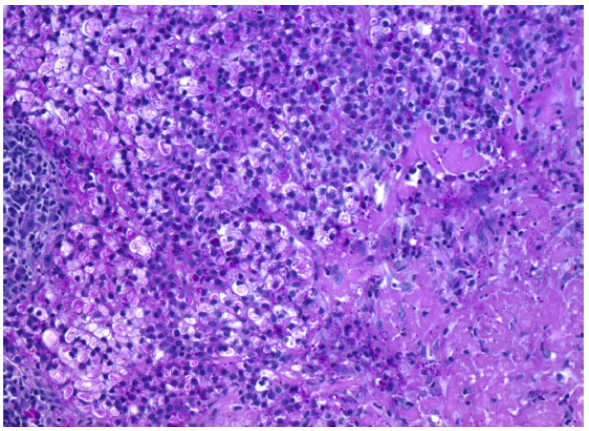

Fig. 3. Nests of clear cells and cells with eosinophilic cytoplasm in a hyalinized stroma (200x, H&E stain)

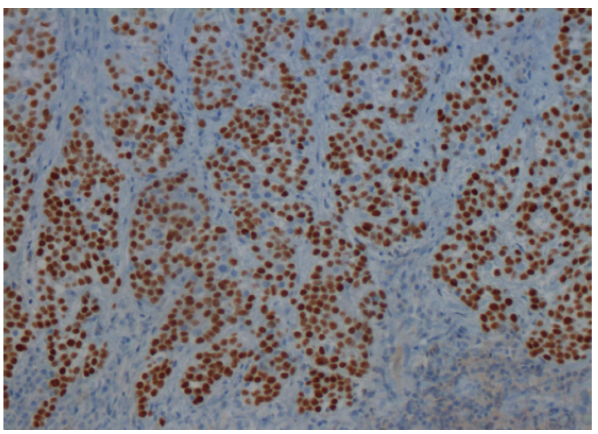

Fig. 4. Positive stain for p63 (200x)

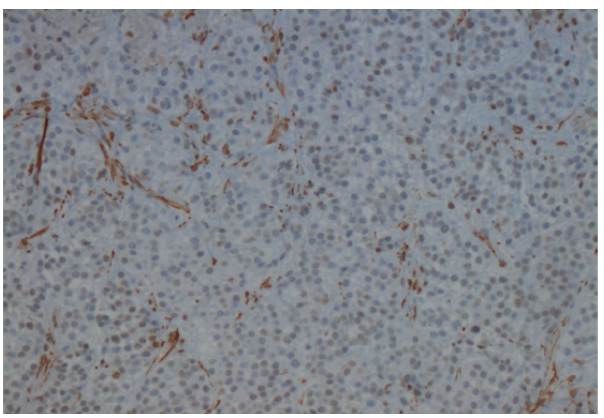

Fig. 5. Negative stain for SMA (200x)

The lymph node has been surgically removed for further examination. Cords and nests of clear cells and cells with eosinophilic cytoplasm in a hyalinized stroma were identified within the lymph node (Figure 3). Immunohistochemical stains were positive for p63 (Figure 4), Epithelial Membrane Antigen (EMA) and negative for Smooth Muscle Actin (SMA) (Figure 5), Melan A, HMB45, De-

smin, PAX8, CD30, Uroplakin, Estrogen Receptor (ER), GCDFP-15, Inhibin, WT1 and Vimentin. Tumor cells were also PAS positive and Mucin negative.

Discussion

When diagnosing HCCC, one must exclude other, more frequent lesions of the oral cavity. Metastatic Clear Cell Renal Cell Carcinoma was taken under consideration at the begining of the differential diagnosis. The sample that was first examined was small and lacked hyalinising stroma. However, metastatic tumor cells from the lymph node were positive for p63 and negative for CD10 and therefore CCRCC was excluded.[11]

Primary oral cavity lesions that present squamous differentiation are squamous cell carcinoma (SCC) with clear cell differentiation and mucoepidermoid carcinoma. SCC presents grater nuclear atypia than HCCC and has a high mitotic activity.[12] Mucoepidermoid carcinoma has a high tendency for cyst formation lined by goblet type mucinous cells and generally lacks sclerosis/hyalinization and small nests or thin cords of tumor.[13] Tumor mimics with myoepithelial differentiation, in particular epithelial-myoepithelial carcinoma usually show expression of markers such as SMA or S-100 Protein which were negative in presented case.[14] Finaly, clear cell odontogenic carcinoma was considered a less likely diagnosis due to lacalization of the tumor.[15] After the diagnosis the patient has been transferred to another Oncology Hospital for further treatment.

Conclusion

The diagnosis of Hylinizing clear cell carcinoma of the salivary gland may be difficult, especially when the examined tissue sample is small and doesn't include all of the components of the tumor. Immunochistochemical stains may be very helpful in such difficult cases. In addition a EWSR1-ATF1 gene fusion seen in fluorescence in situ hybridization (FISH) confirm the diagnosis.

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CASUISTIC PAPER

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Generation of retractive spine circuits in the process of vitamin B12 deficiency

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ABSTRACT

Introduction. Subacute degeneration of the posterior and lateral spinal cord is a rare neurological complication of B12 avitaminosis.

Aim. In this paper, we present the case of a 65-year-old man who, in the course of long-term vitamin B12 deficiency associated with atrophic gastritis, developed a severe set of neurological symptoms that are part of the retinal spinal cord degeneration with characteristic features in MR imaging of the cervical spine in the form of an inverted "V mark" in axial images and typical localization in the spinal cord.

Description of the case. After careful analysis of the syndrome and making an early diagnosis, parenteral vitamin B12 supplementation began, resulting in improved neurological status, laboratory parameters as well as regression of changes in magnetic resonance imaging.

Conclusion Significant symptoms of this syndrome are paresthesia in the distal parts of the limbs, ataxia, spastic paresis.

Keywords. ataxia, B12 avitaminosis, retinal spinal cord degeneratio

Introduction

Vitamin B12 belongs to the water-soluble B group vitamins, this compound is an important cofactor in the metabolism of carbohydrates, fats, amino acids and fatty acids in the human body. The daily requirement for this vitamin is 2 μg/day and 2.6-2.8 μg in pregnant women, but the guidelines for the recommended doses vary from country to country. Cyanocobalamin is stored in the liver, and its deficiencies may appear 3-6 years after taking the last dose with a loss of more than 90% of this vitamin. Absorption of vitamin B12 takes place in the final section of the small intestine, the ileum, after binding to the internal factor produced by the stomach's parietal cells in the presence of calcium ions.[1-6] Vitamin B12 deficiency causes a wide range of hematological, gastrointestinal and neuropsychiatric disorders.

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Symptoms of damage to these systems may occur in varying degrees and form different syndromes. A serious complication of vitamin B12 deficiency is polyneuropathy and spinal cord degeneration.[7-20]

Aim

The aim of this paper is to present a case of retractive spine circuits in the process of vitamin B12 deficiency.

Description of the case

A 68-year-old patient was admitted to the Department because of the progressive weakening of the muscular strength of the lower limbs with accompanying imbalances from 3 months. In addition, from two weeks before the party he complained about the feeling of numbness, awkwardness of his hands, he had difficulty fastening his shirt buttons, writing. He negated the occurrence of sphincter disorders and severe sensory disorders. He has not undergone any infection recently. In history, he was chronically treated for type 2 diabetes (metformin), hypothyroidism, and prostatic hyperplasia. In addition, he underwent L5-S1 discopathy surgery about 20 years ago. Neurological examination at admission showed weak precise hand movements on both sides, medium-degree lower limb pyramidal paresis more severe in the right lower limb with Babinski's identical symptom, impaired sensation of vibration in the upper and lower limbs both proximal and distal, with normal superficial sensation, paraparetic gait with the help of an elbow crutch.[8-12] MRI of the cervical spine was performed, in which, apart from multilevel degenerative-discopathic changes C3-C7, the longitudinal band of the increased signal in the spinal cord was imaged from the C2-C6 stem in T2 and STIR images, showing no contrast enhancement located in the area of the posterior cords myelopathy with a characteristic inverted "V" image in axial images. Basic laboratory tests showed macrocyte anemia - HB levels 10.7 [g/dl] [min: 13.7 max: 17.5], MCV 109.7 [fl] [min: 79 max: 92.2 F], deep vitamin B12 deficiency <83 [pg / ml] [min: 189 max: 883 F:] with normal levels of folic acid and iron. After completing the patient's medical history, the B12 deficiency was found 4 years ago, the patient stopped supplementation after a few months. Differential diagnostics also included primary demyelination and infectious causes. PMR was obtained in which no oligoclonal bands and anti-Lyme disease anti-Lyme Bodies were found in IgM and IgG. In the PMR general study, no significant irregularities were found. HIV and VDRL tests were negative. Glycated hemoglobin was normal. No anti-aquoporin 4 bodies were found in serum. The ENG study of nerve conduction revealed chronic axonal sensory-motor polyneuropathy. Gastroscopy showed atrophic gastritis, gastroesophageal reflux disease, histopathological grade II metaplasia. Diagnosis of spinal cord degeneration against vitamin B12 deficiency was made. Parenteral vitamin B12 supplementation was implemented for treatment. He was discharged to the Rehabilitation Department for further improvement. The patient was re-admitted to the Department of Neurology after 5 months to re-evaluate and perform follow-up tests: a significant improvement in the neurological condition was clinically observed, no weakening of the muscular strength of the lower limbs or pyramidal symptoms was observed, the patient was able to walk alone, on a broad basis, the study returned attention to ataxia from the lower limbs, as well as persistent disturbances of deep sensation, however, to a lesser extent than previously noted. Laboratory tests showed an improvement in blood count parameters. The MR examination of the cervical spine compared to the previous examination showed a clear regression of the previously described changes in the spinal cord. The patient is currently undergoing maintenance treatment with vitamin B12 1000ug /month. In addition, it awaits the control of the Gastroenterology Clinic.

Discussion

Cord degeneration of the spinal cord refers to degenerative disease of the central and peripheral nervous system damage, pathological changes in the spinal cord more often involve white matter than gray matter. More often than the loss of axons, a symmetrical absence of myelin sheaths is observed, the changes are most noticeable in the posterior and lateral cords.[12-21] SCD is a rare neurological complication of vitamin B12 deficiency in the body, it occurs most often around 50 years of age, this disease is rarer seen in younger people, very rarely in children. Symptoms of severe damage to the nervous system are now rare. Early diagnosis and the possibility of successful treatment reduced the number of patients with cord degeneration.[14] The most common causes of B12 avitaminosis are malabsorption (e.g. pernicious anemia, gastrectomy, bariatric surgery, ileum resection, congenital Castle internal deficiency, gastritis caused by *H. pylori*, Lesniowski and Crohn's disease, non-immunological) chronic atrophic gastritis, chronic pancreatitis, congenital selective absorption disorders, Zollinger-Ellison syndrome, bacterial hyperplasia syndrome, congenital metabolic disorders, including transcobalamin deficiency), interactions between vitamin B12 and chronic medications (e.g. metformin, medications hydrochloric acid secretion, nitric oxide), insufficient food intake (veganism or vegetarianism, malnutrition, alcoholism).[5,6,11,19] Clinical symptoms of cobalamin deficiency usually appear in the chronic period of 3-5 years after the occurrence of absorption disorders or lack of it in food. The body has a large supply of vitamin B12 estimated at about 1-10mg (mainly liver) and a mechanism for saving this vitamin, which consists

in the reabsorption of bile secreted cobalamin from the gastrointestinal tract.[5] Pearce and other colleagues also emphasize the important role of nitrous oxide in their work, which due to the possibility of rapid inactivation of vitamin B12 may cause the development of SCD symptoms in a few weeks.[4] To quote Merrit, a single dose of anesthetic in a susceptible person or chronic exposure usually associated with intoxication with gas available in dental offices or other treatment rooms or commercially available may lead to vitamin B12 deficiency.[17] Haematological disorders are not normally associated with nitrous oxide abuse. Vitamin B12 deficiency in most patients is asymptomatic, it is thought that 40% of all patients with vitamin B12 deficiency have neurological problems or symptoms and are often the first symptoms of the disease.[17] The clinical picture of SCD consists of signs of damage to both posterior and lateral scars. Significant symptoms of this syndrome are paresthesia in the distal parts of the limbs, ataxia, spastic paresis. Therefore, there is a combination of pyramidal symptoms with sensory symptoms of varying severity, namely in some cases pyramidal over sensory symptoms predominate and in other sensory symptoms over pyramidal symptoms. Sphincter disorders are rare, usually occur late in untreated patients. Middle darkness without changes at the fundus and optic atrophy are very rare symptoms.[13,14] In the presented clinical case, the patient due to malabsorption due to atrophic gastritis confirmed by gastroscopy and long-term vitamin B12 deficiency developed a severe mixed neurological disorder syndrome, in which spastic paresis of the lower limbs dominated with pyramidal symptoms with less pronounced impairment of deep sensation and ataxia . The above syndrome with symptoms of severe damage to the nervous system is currently rare.[12-15] Diagnosis of SCD is primarily based on demonstrating a reduced level of vitamin B12, some patients with low levels of vitamin B12 do not have a deficiency of it, then additional tests may be useful. Methylmalonic acid and homocysteine accumulate as a result of impaired cobalt-dependent biochemical reactions. Abnormally high levels of both of these substances can be found in serum in more than 99% of patients. These studies have limited utility in some populations, as increased homocysteine occurs in hereditary hyperhomocysteinemia, and increased concentration of methylmalonic acid in patients with renal failure. Of the patients with neurological symptoms, only 20% have severe anemia. Both hematocrit and mean corpuscular volume may be normal, although macrocytic anemia is a classic abnormality found in this deficiency.[17] Other ancillary tests used in the diagnosis of cobalamin deficiency may be electoneurographic tests or magnetic resonance imaging (MR).Regarding magnetic resonance imaging, only 11.1% to 36.7% of patients show characteristic abnormalities.[3] The results of MRI in SCD are extremely diagnostic and even pathognomonic. MR shows a very typical pattern with hyperintensive changes in sequences. T2 dependent usually limited to the posterior and/or lateral columns of the spinal cord, most often located in the range of the lower cervical and thoracic sections. On the axial cross-sections characteristically adopting the characteristic "inverted V" sign, "pair of binoculars", "dot sign".[3-10] In the presented clinical case of a patient of our Ward in a radiological examination, the pathological band of the increased signal was depicted in the T explain sensory-motor disorders occurring in a neurological examination.[11-17] The characteristic location of lesions in the spinal cord is typical for B12 avitaminosis. As mentioned in the work of Ravina et al. MR also seems to be a good diagnostic tool also for assessing the control effectiveness of treatment.[10] It was found that younger age <50 years with shorter disease duration, changes in MR involving <7 core segments are associated with a higher probability of a positive treatment outcome. However, diagnostic delay or late start of treatment can cause permanent spinal cord injury with little or no improvement. Another auxiliary study in B12 avitaminosis is an electroneurographic study, in which features of sensory-motor polyneuropathy with a predominance of sensory symptoms can be found, and the ENG picture corresponds to axonal neuropathy.[17-18] Also, the patient presented above revealed characteristic features in the ENG study. Peripheral neuropathy may be mistakenly diagnosed as diabetic neuropathy, and further failure to recognize the cause may further damage central nervous system function.[5] Differential diagnosis of SCD can be broad and can include nutritional deficiencies (copper deficiency, vitamin E), demyelinating processes (MS), infectious causes (HIV vaculopathy, herpes), inflammatory processes (sarcoidosis), ischemic and cancer (astrocytoma and ependymomas), syndromes hereditary (Fredreich's ataxia, Leukoencephalopathy with brainstem and spinal cord involvement).[9] In the presented patient in differential diagnosis, mainly demyelinating and infectious processes were taken into account, however, macrocytical anemia with deep vitamin B12 deficiency and characteristic changes in MR imaging present in the basic studies with significant improvement after the treatment was associated with confirmation of the diagnosed diagnosis of cord degeneration of the spinal cord and did not require further differentiation. Treatment of vitamin B12 deficiency should be started as early as possible. It should include causal and substitution treatment. For the degeneration of the spinal cord, we use cyanocobalamin at a dose of 1000 μg administered intramuscularly every other day until the symptoms have disappeared, then a monthly maintenance dose of 1mg for life, in addition to vitamin B12 deficiency therapy, appropriate dietary recommen-

dations should also be implemented, i.e. a rich diet in animal protein. [6,19,20] After parenteral administration of vitamin B12, hematological improvement may be evident after 48 hours, there is also a subjective improvement in well-being. Paresthesia is the first neurological ailment that regresses (within the first 2 weeks), cortical and cognitive disorders respond more slowly usually over 3 months, further improvement in clinical condition may take up to a year. If there is no response to treatment after 3 months, the disorders are probably not due to vitamin B12 deficiency. About half of the patients have some abnormalities found in physical examination.[17] In the presented patient, after 5 months of treatment, a clear but incomplete improvement of the neurological condition was found, first of all an improvement in motor functions was achieved, thanks to which the patient is able to move independently, moreover, an improvement in blood morphotic parameters, as well as a marked regression changes in resonance imaging.[18-20]

Conclusion

Subacute degeneration of the posterior and lateral spinal cord is a rare neurological complication of B12 avitaminosis. In this paper, we present the case of a 65-year-old man who, in the course of long-term vitamin B12 deficiency associated with atrophic gastritis, developed a severe set of neurological symptoms that are part of the retinal spinal cord degeneration with characteristic features in MR imaging of the cervical spine in the form of an inverted "V mark" 'in axial images and typical localization in the spinal cord. After careful analysis of the syndrome and making an early diagnosis, parenteral vitamin B12 supplementation began, resulting in improved neurological status, laboratory parameters as well as regression of changes in magnetic resonance imaging.

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CASUISTIC PAPER

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Diagnostic and therapeutic difficulties of tick-borne encephalitis – a two case reports

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ABSTRACT

Introduction. The paper presents epidemiology, routes of infection, forms of the disease, diagnostic and treatment methods, and prophylaxis of tick-borne encephalitis.

Aim. In this paper, we present two descriptions of the cases of tick-borne encephalitis.

Description of the cases.

Case 1. A 60-year-old man with fever up to 39 degrees for 3 days, multi-site headache and other body aches, as well as an ear-stuck feeling. The day before hospitalization, there was a feeling of numbness on the right side of the face from eye level to the chin and speech distortion.

Case 2. A 60-year-old patient with headaches and an increase in temperature to 39 degrees for 3 days, who, approximately, three weeks earlier was ticked by a tick in the lower parts of the back.

Conclusion. It is also important for doctors to take a broader view and to make society aware of that Lyme disease is not associated only with Lyme disease. Further work is also needed towards effective treatments for Tick-borne encephalitis (TBE).

Keywords. diagnostic, tick borne encephalitis, treatments

Introduction

Tick-borne encephalitis (TBE) is still a significant diagnostic difficulty due to the lack of specific symptoms. Another problem is the lack of effective treatment for the disease. Currently, the only effective method of preventing disease is vaccination. Tick-borne encephalomyelitis also called Central European Encephalitis (CEE), Russian Spring-Summer Encephalitis (RSSE), tick borne encephalitis (TBE) to flavivirus disease (TBEV) from the Flaviviridae family, which belongs to the group of arboviruses.[1] In Europe, two subtypes of this virus are distinguished: eastern, which is transmitted by Ixodes

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persulcatus ticks and causes Russian spring-summer encephalitis, and western (European) that causes Central European encephalitis, transmitted by ticks of the species Ixodes Ricinus.[2,3] It is the latter species of the tick that is most important in Poland in the spread of the TBE virus from an infected animal to a human.[4,5]

In endemic areas of Europe, the percentage of infected ticks varies between 0.5-5%. Incidence occurs seasonally, in spring and summer, when tick feeding is intensified.[4] Currently in Poland, the number of cases of full-blown TBE over the past 10 years is estimated at 150 to over 250 cases per year. In 2014, 195 cases were recorded, and in 2015, 150 cases of TBE Epidemiological studies show that these are underestimated data.[5] The highest risk of illness is observed in northern, northeastern and eastern Poland. Exposure to tick sting is particularly beneficial for some professions. This risk group includes forest workers, farmers (especially those who have farms located in close proximity to forests), people dealing in collecting undergrowth, but also border guards patrolling border areas.[6] It is worth emphasizing that people professionally involved in working in the forest can be naturally immunized as a result of numerous tick bites and the introduction of minimal, subliminal doses of TBE virus that do not cause disease symptoms, but induce the production of specific antibodies.[7] Human infection most often occurs as a result of pricking by an infected tick (the virus is transmitted along with its saliva during blood suction). In addition, infection can occur through the digestive tract by consuming raw, unpasteurized milk and milk products (yogurt, cheese, butter) from infected animals, i.e. cows, sheep, goats.[8,9] The existence of this route of infection is due to the fact that the virus can penetrate from the blood into the mammary glands of infected animals, and also remains active in an environment at pH 2.75-11.55 for about 24 hours, and therefore is not inactivated in the stomach. According to studies, TBEV retains the ability to virulence in the milk of infected animals for up to 8 days.[9,10] In milk, butter or cheese, the virus can survive for many months. Pasteurisation of dairy products provides full protection against infection, because TBEV is sensitive to temperature changes.[11,12] As a result of transmission of the virus through the digestive tract, a characteristic form of the disease may develop, i.e. biphasic milk fever. This type of infection accounts for around 10-20% of all TBEV cases in Europe.[9] Occasionally, infection can also occur through the inhalation route through the olfactory epithelium when inhaling the suspension of viral particles, since it has been proven that the virus remains infectious in air for up to 6 hours at room temperature.[12] In addition, cases of infections due to cuts during laboratory work and transfusional infections have been described.[13,14] The virus is not transmitted from person to person. The incubation period of the KZM virus is from 7 to 14 days after a tick bite, and from 3 to 4 days in the case of gastrointestinal infection.[14-17] Sensitivity to infection is common, but the disease is usually asymptomatic.[4] Central European tick-borne encephalitis has a two-phase course.[4] The first phase of the disease lasts on average 4 days (1-8) and is characterized by a sudden onset. It is associated with the virus getting into the blood after being pricked by an infected tick. Wiremia is accompanied by an increase in body temperature not exceeding usually 38°C, less often reaching 40°C with non-specific flu-like symptoms, i.e. malaise, increased psychophysical fatigue, increased sweating, headache, nausea and vomiting, muscle and joint pain, photophobia, catarrhal upper respiratory tract, conjunctivitis. Some patients may have a maculopapular rash mainly on the torso. During this period, leukopenia and thrombocytopenia, as well as an increase in CSB albumin can be observed in laboratory tests.[8] In about 13 -26% of infected, the disease ends with the first phase, followed by recovery and in the remaining patients (about 74-87%), usually after an average of 8 days (1-33) of well-being, the second phase of so-called neurological.[18] 23-50% of patients only have symptoms of the second phase of the disease without first phase symptoms.[11,19] The neurological phase is associated with the entry of the virus into the central nervous system. Again, body temperature rises 39-40°C. There are severe headaches, nausea, vomiting, meningeal symptoms and muscle and joint pain.[8] Depending on the location of the inflammatory process in the central nervous system (CNS) and the clinical picture of the disease, the following forms of KZM can be distinguished: meningitis, encephalomyelitis (encephalomeningitis), meningitis, encephalitis and spinal cord (meningoencephalomyelitis), meningitis, encephalomyelitis (meningoencephaloradiculitis).[8] The meningeal form is the most common, occurs in about 49% of patients, has the mildest course. Symptoms are typical for lymphocytic meningitis. A more severe course is characterized by meningitis. In its course may occur: ataxia, disturbances of consciousness up to and including coma, sometimes cranial nerve palsy. About 10% of patients suffer from the most severe meningitis. It leads to anterior horns of the spinal cord and flaccid limb paralysis. Positive meningeal symptoms, symptoms of focal CNS, nerve roots and peripheral nerves are found.[8] Prognosis worsens the involvement of the medulla and brainstem. KZM mortality is up to 5% .[8] Most patients recover fully. In some cases, there is a prolongation of the disease process and its transition into a chronic form with periods of disease progression and its stabilization.[20-22] A lighter course is usually more common in children and adolescents than in adults. In people over 60 years of age, the course of KZM is usually more severe and sometimes leads to permanent neurological or psychological consequences. The frequency of neurological complications is estimated at 20-50%.[8] The most common among them are: paralysis or paresis of

cranial nerves, multi-nerve damage with paralysis of various muscle groups - most often the shoulder belt with muscle atrophy, mainly deltoid muscle, flaccid paralysis of the limbs, damage to the cerebellum (gait and speech disorders, nystagmus, intentional tremor), sensory disorders, neuralgia, focal or generalized epileptic seizures, intellectual disorders: concentration disorders, attention, persistent and fresh memory, perception (hallucinations), thinking (delusions), mood and emotions (depression, mania, anxiety) or personality and behavioral disorders and insomnia.[8,22-25]

The basis for diagnosis is the detection of specific antibodies in the IgM and/or IgG class in blood serum and pmr by ELISA.[8] IgM antibodies are detected in the serum of patients with TBE after about 7-10 days from the time of infection and they persist for an average of 40 days, and IgG antibodies appear later, about 14 days after the infection, but they can be detected in serum up to several dozen years after infection. It should be noted that usually in routine diagnostics of TBE with developed TBEV-induced neuroinfection both of the abovementioned classes of antibodies are detected simultaneously. In the cerebrospinal fluid, however, in patients with active TBE, specific IgM and IgG immunoglobulins appear later than in the blood and are detected for a shorter time than when they are present in the serum.[7] It is also possible to demonstrate the genome of the TBE virus by RT-PCR (reverse-transcriptase polymerase chain reaction) in serum and CSF in the acute phase of the disease. This is of little importance in routine diagnostics, because in the neurological phase, which usually occurs during the hospitalization period, the virus is already absent in serum and in CSF.[8] The CSF general examination is important in the diagnosis of TBE Inflammatory changes in PMR usually persist for 4 to 6 weeks, less often for several months in the form of increased protein and cytosis.[26-28] It should be noted that the lack of characteristic epidemiological data in the patient's history (tick bite, seasonality) does not allow the exclusion of any tick-borne disease.[4] When TBE is found, only symptomatic treatment is used. It involves the administration of antipyretic, analgesic, anti-inflammatory, anti-edema drugs, and in severe cases also glucocorticosteroids.[29] The most effective form of prevention is vaccination.

Aim

In this paper, we present two descriptions of the cases of tick-borne encephalitis.

Description of the cases

Case 1.

A 60-year-old man was admitted to the Department of Neurology with the following symptoms: fever up to 39 degrees for 3 days, multi-site headache and other body aches, as well as an ear-stuck feeling. The day before hospitalization, there was a feeling of numbness on the right side of the face from eye level to the chin and speech distortion. About 5 days before hospitalization, the patient ended 10-day antibiotic therapy due to upper respiratory tract infection. In addition, about 3 weeks earlier he was ticked by a tick around the lower parts of the back without extensive erythema. Upon admission to the Department by neurological examination for deviations from the normal state, it was found: somewhat dysartic speech, distortion of the sensation from the height of the eye socket down on the right side of the face, smoothing of the right nasolabial fold, weaker tooth grinding on the right, the patient was not upright. Computed tomography of the head performed in the urgent mode, transthoracic echocardiography of the heart and laboratory tests did not reveal any significant deviations from the norm. Pre-diagnosed neuroinfections. Lumbar puncture was performed, cerebrospinal fluid was taken for general examination and Borrelia burdorferii antibodies in the IgM and IgG class (negative results were obtained in the following days of hospitalization). The pmr study found: a slightly increased protein level of 55.7 mg / dl, pleocytosis of 37 cells /mcl, percentage of cells with a monoplane nucleus 41%, multiplane 59%. Due to the features of V and VII neuropathy of the cranial nerve, diagnostics was expanded to include magnetic resonance imaging of the head with contrast. The study describes on average numerous (about 20) hyperintensive foci in the T2 and Flair sequences, invisible in the T1 and DWI sequences, not enhancing the signal after the contrast agent - most likely foci of deep white matter ischemia for differentiation with demyelinating lesions in both frontal and parietal lobes. In addition, old painting pits in the left parietal lobe, amygdala and bridge were described. On the basis of the overall clinical picture, acute meningitis and encephalitis were diagnosed, most likely of viral etiology. Antiviral and anti-inflammatory treatment was implemented - acyclovir and dexamethasone Otolaryngological consultation was performed due to the patient's feeling of tapping in the ears and the features of damage to the right nerve of the VIIth patient. The study did not find an ear-like aetiology of the aforementioned ailments, further treatment in the Department of Neurology was recommended. On the first day of hospitalization, the patient continued to fever to approximately 39.2 degrees. There was a sharp deterioration in the general and neurological condition. The patient reported shortness of breath, feeling cold, and general weakness. Swallowing difficulties arose as a result of which the patient choked. Chest x-ray (x-ray of the klp) was taken - no pathology. The patient was moved to the intensive neurological supervision room and monitoring of vital functions began. In the neurological examination, the previously described deviations involuntarily joined face movements mainly around the mouth, grunting, nystagmus when looking to

the right, paresis of the right side of the face, facial muscles, paresis of the palate, throat and tongue, paresis of the middle right upper limb, weakness of hand grip after right. Urgent head magnetic resonance imaging was ordered, excluding fresh ischemia. The image showed no significant differences compared to the previous study. In the following hours the patient's general condition continued to deteriorate rapidly. Due to acute respiratory failure, the patient was intubated and transferred to the Anaesthesiology and Intensive Care Unit (ICU). After admission to the above-mentioned ward, the patient's condition remained severe. The fever was up to 38.2 degrees. The patient was connected to a respirator. He required analgosedation, dopamine infusion for hypotension and stimulation of furosemide diuresis. Bilateral inflammatory changes of the lungs, probably after aspiration, have been reported in the x-ray of the klp. Antiviral treatment was maintained. Antibiotic therapies were used with good effect (in the X-ray of the chest, the complete regression of the inflammatory changes previously described was seen). In the following days the patient's neurological condition continued to deteriorate. During the entire hospitalization at the ICU, the patient was consulted neurologically several times. The next neurological examination revealed: medium-wide pupils, poorly responsive to light, trace corneal and ciliary reflexes, no ocular-head reflex. Periodic involuntary serial movements of the supraorbital region, lips and tongue, flaccid paralysis with extremely weak deep reflexes and lack of plantar reflexes. In control computed tomography of the head, fresh pathologies within the brain were excluded. The patient was consulted by a doctor of Infectious Diseases, diagnostic recommendations were implemented. In the differential diagnosis of symptoms presented by the patient, Guillain-Barry syndrome (Miller-Fischer variant), autoimmune encephalitis, subacute sclerosing encephalitis (SSPE), neuroborreliosis, tuberculosis of the nervous system, tick-borne encephalitis (KZM) were taken into account. Therefore, CSF was again collected for general examination, virological and anti-neuronal antibodies. Anti-neuronal antibodies and antibodies against GM1 and GQ1b gangliosides were determined in the blood. Re-examination of the cerebrospinal fluid showed slightly increased pleocytosis (8 cells/mcl) and high protein levels (313.4 mg/dl) - features of protein-cell cleavage. In this situation, taking into account the clinical picture together with the results of the CSF, suspected acute inflammatory polyradiculoneuropathy - Guillain-Barre syndrome with a possible Miller-Fischer variant. High doses of intravenous glucocorticosteroids were used followed by intravenous infusion of immunoglobulins without the expected clinical effect. In connection with the above, 5 plasmapheresis procedures were performed. Despite the treatment, the patient was still in a severe general condition. In a non-contact neurological examination, eyes opened spontaneously, four-limb limp paresis. On the 16th day of hospitalization, the ENG examination was performed, which did not show the characteristics of acute inflammatory radiculoneuropathy. The study found features of a significant degree of nerve damage at the trunk level in the area of sensory and motor fibers, which gave a picture of sensorimotor polyneuropathy mainly of an axonal nature with a demyelination component. In the performed electroencephalographic examination, an abnormal, encephalopathic record was found. On the 23rd day of hospitalization, results of tests for KZM were obtained - anti-TBEV antibodies: positive in the IgM class 4.27 and border IgG 1.02 (descriptive norm: <0.8 negative, 0.8-1.1 border > 1,1-positive). Based on the results of laboratory tests, presented by the patient's symptoms and medical history, tick-borne meningitis, encephalomyelitis was diagnosed. Due to the lack of effective causal treatment, supportive treatment was carried out. In the next days of hospitalization the patient's condition remained very severe. On the 36th day of hospitalization, the patient experienced tremors of facial mimics. Neurologically consulted. The study found: residual elements of consciousness, lying patient, the only motor activities are partial opening of the eyelids, periodic facial grimaces, periodic symmetrical series of myoclonic seizures of both cheeks and upper lips, scanty movements of tongue tightening, periodic floating eye movements to the sides, knobs eyes set straight ahead, in a slight divergent strabismus, medium wide pupils, symmetrically correctly responsive to light, corneal and ciliary reflexes preserved, symmetrical, ocular-head reflex absent, assisted breathing, tracheostomy, unable to swallow and effective expectoration of upper respiratory tract secretion , nourished by PEG, suctioned, flaccid four-limb paralysis with no deep and plantar reflexes - areflexia, Babinski's symptom and foot-shake bilaterally absent. Symptomatic epilepsy was diagnosed in the form of myoclonic seizures on both sides of the face, most likely a consequence of KZM. Sodium valproate with valproic acid was successfully added to anti-epileptic treatment. Attempts to disconnect the patient from the ventilator have been unsuccessful. After gaining relative circulatory and respiratory stability of the patient in a vegetative state, he was transferred to the Care and Treatment Institution.

Case 2.

A 60-year-old patient who, approximately 5 days before hospitalization, ended ten-day antibiotic therapy due to upper respiratory tract infection. In addition, about three weeks earlier he was ticked by a tick in the lower parts of the back. He did not observe the presence of typical erythema. At the time of admission to the Department of Neurology, he gave a number of non-specific symptoms, including headaches and an increase in temperature to 39 degrees for 3 days. To confirm the initial diagnosis of

meningitis of cerebrospinal fluid, cerebrospinal fluid in which pleocytosis was found - 37 cells/mcl, including the percentage of cells with a monoplane nucleus 41%, multiplane 59%. Acyclovir antiviral treatment was introduced. Due to the rapid progression of neurological symptoms and the increase of respiratory failure, the patient was intubated and transferred to the Anaesthesiology and Intensive Care Unit (ICU). During hospitalization at the ICU, the patient was in a very severe general condition, unaware, with a limb four-limb paresis. In the differential diagnosis of his symptoms, Guillain-Barry syndrome (Miller-Fischer variant), autoimmune encephalitis, subacute sclerosing encephalitis (SSPE), neuroborreliosis, tuberculosis of the nervous system, tick-borne encephalitis (TBE) were taken into account. On the 10th day of hospitalization, in the re-examination of the cerebrospinal fluid, features of protein-cell cleavage (pleocytosis 8 cells/mcl, protein 313.4 mg/dl) were found. Intravenous glucocorticosteroids were included in the treatment followed by intravenous infusion immunoglobulins. In the absence of a therapeutic effect, it was decided to terminate the administration of immunoglobulins and 5 plasmapheresis treatments performed - without a therapeutic effect. On the 16th day of hospitalization, an electroneurographic examination (ENG) was performed, which did not show the characteristics of acute inflammatory radiculoneuropathy. In the following days, the patient required tracheostomy and percutaneous endoscopic gastrostomy (PEG). On day 23 of hospitalization, a positive test for IgM and IgG against TBE virus was obtained. Based on the overall clinical picture and history, severe postinflammatory encephalopathy was diagnosed as a consequence of tick-borne encephalitis. On the 36th day of hospitalization, the patient felt shaky facial mimics. Symptomatic epilepsy was diagnosed in the form of myoclonic seizures on both sides of the face - a possible complication of TBE.

The reason for conducting extensive differential diagnosis in the described patient before proper diagnosis of tick-borne encephalitis is the fact that this disease can cause a number of non-characteristic symptoms, especially at the initial stage. An additional difficulty is the fact that patients often do not notice tick ticks because tick saliva has anesthetic properties.[19,23] Both patients and doctors first consider the possibility of Lyme disease as the most common and most common tick-borne disease. The presented patient should be suspected that the first phase of the disease occurred before hospitalization and was in the form of upper respiratory tract infection. The reason for reporting and admission to the Department of Neurology were mainly severe headaches, high temperature and features of V and VII cranial nerve neuropathy, which were the expression of the beginning neurological phase of KZM. Unfortunately, the patient developed the most severe form of the disease, namely meninges and spinal cord involvement with cranial nerves and the medulla oblongata. Undoubtedly, the patient's advanced age affected such an abrupt and severe course of the disease. Due to the lack of effective treatment, only symptomatic treatment is possible, and the prognosis for further survival is uncertain due to the occurrence of numerous complications: respiratory failure, swallowing disorders, flaccid paralysis, consciousness disorders and symptomatic epilepsy. Due to the great diagnostic difficulties of KZM and the complicated and not always effective methods of treating this disease, it is always worth considering the use of prevention. Its most effective form is the use of passive or active immunization. Two inactivated vaccines with similar composition are available in Poland. They can be used even in states of impaired immunity. The full vaccination course includes three basic doses (second dose after 3 months and another 9 to 12 months after the first) and one booster dose every 3-5 years.[30] Inoculation in winter or early spring provides protection from the beginning of tick activity (from April to October). The vaccine is safe, according to the literature, undesirable vaccination symptoms are very rare and disappear on their own. This vaccination is particularly recommended in specific professional groups and for people staying in endemic areas. Vaccines against tick-borne encephalitis are highly effective - for every 100 people vaccinated over 95, they produce specific protective antibodies that protect against complications. Passive immunization, on the other hand, consists in administering immunoglobulin against the KZM virus up to 96 hours after tick insertion, which aims to obtain immediate immunization of seronegative persons.[5,30-32]

Conclusion

The described cases show how important it is to spread the principles of prevention and the need for preventive vaccinations, especially among people from endemic areas and professions from high risk groups. The basic way to prevent getting TBE is to avoid situations where you may be exposed to a tick by a tick (primarily wearing clothing that protects against getting ticks on your skin). Clothes can be sprayed with permethrin. On exposed parts of the skin outside the face, you can apply so-called repellents (e.g. DEET-N, N-diethyl-meta-toluamide). After staying in tick feeding places, you should carefully examine the skin and to be sure, wash the whole body in the shower with a soft brush. The ticks that are stuck in the skin are removed immediately after being noticed, preferably with tweezers, and the place after the injection should be decontaminated. Pharmacological prevention of the disease is also important.

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CASUISTIC PAPER

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Brachial artery injury

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ABSTRACT

Introduction. Arterial damage associated with musculoskeletal injuries at room conditions is very common.

Aim. It is worth remembering that examining a patient who has suffered an accident with a broken bone or traumatic joint dislocation may be accompanied by vascular damage. A dislocation or fracture often masks damage to the artery.

Description of the case. In this paper, a 20-year-old patient being a passenger suffered upper right limb trauma in a car accident.

Conclusion. The effects of vascular injuries appear only after a few hours after setting the fracture. It is not known then whether the artery was damaged at the same time with the fracture, whether the injury occurred during the adjustment, or whether the ischemia is finally the result of the pressure exerted by too tight plaster casts.

Keywords. broken bone, traumatic joint dislocation, vascular injuries

Introduction

Penetrating injuries, i.e. open ones, are much more common than closed ones and they are divided into: lateral wounds, transverse cuts and rupture of the artery. Gunshot wounds require additional discussion. Lateral wounds account for 60% of arterial injuries observed during the peace period. In the case of lateral injuries, which are the most common in peacetime, a significant vasoconstriction occurs, causing the bleeding to increase. In a cut artery, most often with a knife, the edges of the wound are even and shrinkage of the artery results in a decrease. The artery rupture occurs as a result of extensive open injuries (e.g. traffic, industrial accidents). The edges of the wound are jagged, the inner membrane curls inwards, which promotes thrombus formation. Vessel bleeding stops. It should be remembered that thrombi periodically stopping bleeding, after withdrawal of the spasm and resolution of the shock, may be squeezed out of the lumen of the artery, resulting in secondary bleeding. Gunshot wounds are characterized by numerous changes in the areas of the primary projectile channel, which is associated with high kinetic energy of the projectile. There are considerable pressure fluctuations in this channel, which can lead to cracks and detachment of the intimal membranes often far away from the bullet path. Blunt injuries, i.e. closed arteries, are divided into bruises, dissections, adventitious cracks and spasm of the vessels.[1-4] They are a consequence of blunt direct and indirect injuries and are characterized by the absence of coating wounds. Symptoms of vascular dam-

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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age can be divided into "large" and "small" ("hard" and "soft" signs) Symptoms of "large" are bleeding, massive hematoma, features of peripheral ischemia of the limb - coldness of the limb, no sensation, no pulse distal to the site of injury.[1-4] All these symptoms can occur at very low intensity or, as in the absence of a pulse on the perimeter, do not occur. We then talk about the symptoms of so-called "Small", i.e. heart deficit without limb ischemia, local hematoma and neurological disorders associated with other injuries, e.g. bone fractures. Shrinking of the ends of the vessel, the formation of thrombi may result in slight bleeding from the vessel. Good collateral circulation can compensate for the lack of blood flow through the axial vessels, which results in resting limb with weakly discernible symptoms or lack of ischemic features. Also, collateral circulation in some arteries may be responsible for the presence of a pulse around the perimeter, of course with slightly less filling.[1-4]

Aim

The paper presents the diagnosis with the subjective and physical examination.

Description of the case

A 20-year-old patient being a passenger suffered upper right limb trauma in a car accident. The orthopedist found a posterior dislocation of the right elbow with avulsive injury to the anterior elbow bag. He repositioned a dislocation under general anesthesia. However, he also noticed symptoms of acute right upper limb ischemia. Urgent vascular surgeon was asked to consult. Acute post-traumatic ischemia of the right upper limb was confirmed suspecting the right brachial artery injury by double imaging. After taking tests and securing blood for a patient qualified for urgent surgery (Figure 1). A transverse incision in the elbow with a proximal extension on the frame after the evacuation of the hematoma was found to tear the brachial artery with a distal adnexal fracture of the distal and proximal part and with a defect of about 10 cm artery. Extensive damage to the brachial veins at the site of injury was also found, which was ligated. Due to extensive damage to the elbow and muscles, orthopedic intervention was requested. The primary repair was the avulsive injury of the right elbow anterior bag. An elbow sac cap with a Wedge Anchor titanium anchor with Force fiber sutures was also sewn in. The collateral ligaments were left for secondary reconstruction. After dissection and refreshing of the brachial artery margins, arterial segments with subadventional rupture were removed (Figure 2). Thrombectomy of the Fogarty catheter in the distal and proximal brachial artery was performed, resulting in good outflow and inflow of the brachial artery. The ulnar vein was removed and a number of anastomoses of the superficial veins in the elbow had been found, which should ensure sufficient blood outflow from the arm. However, with elbow flexion movements, a haemodynamically significant drop in arterial flow was found in intraoperative Doppler ultrasound. Brachial artery ends were dissected and freed again. The span was shortened and slightly displaced, which resulted in better flow after bending the right elbow. Doppler ultrasound examination showed two-phase and high resistance flow.

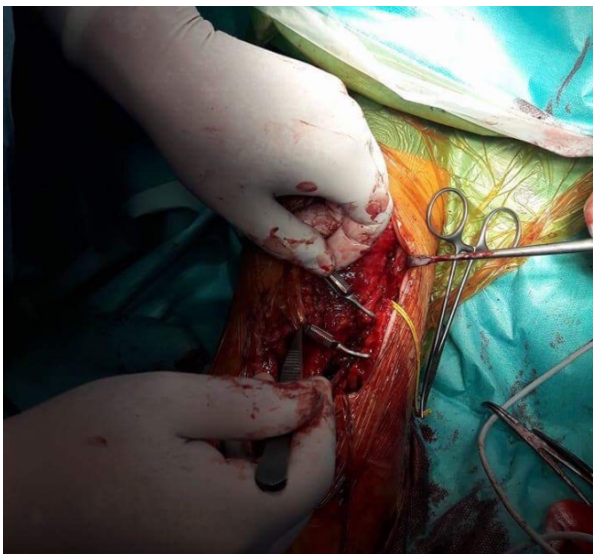

Fig. 1. Rupture of the brachial artery with visible defect despite dissection and activation of the vessel ends

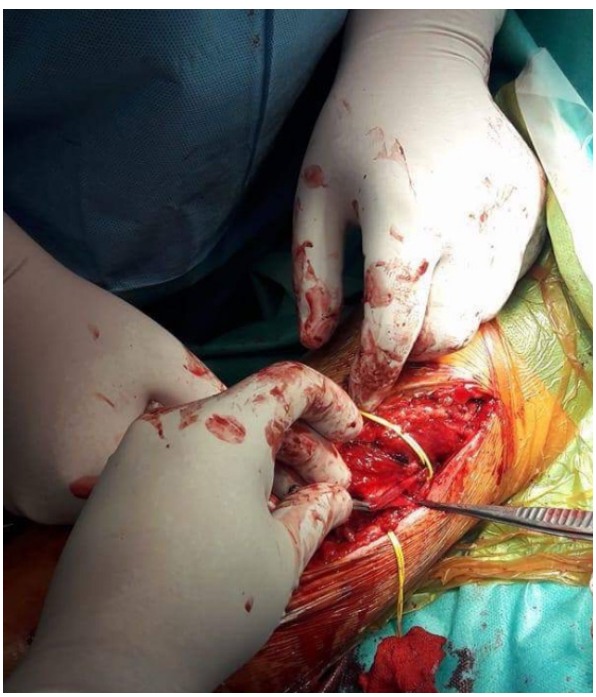

Fig. 2. Just before removing the vascular clamp to activate flow through the brachial brachial bridge

The course of postoperative treatment without major complications. At first, the patient felt only numbness of the fingers and slight swelling of the forearm.

Warming and blood supply to the right upper limb normal. The pulse was well felt on the radial and ulnar arteries. Active finger movements and sensation preserved. The patient had a fixation brace on. The patient was discharged with the wound during normal healing. The patient reported for control- 7 days, 1 month, 3 months, 6 months after discharge from the hospital. The patient had sutures removed on the 12th day after surgery, the splint was removed a month after leaving the hospital. During follow-up examinations, the blood supply did not deteriorate, the feeling of numbness in the fingers of the right hand subsided. Contracture in the elbow and the weakness of the right arm muscle lasted for a long time. However, thanks to the implemented rehabilitation, the range of motion in the elbow and the degree of muscle strength improved significantly. Forearm swelling persisted for up to 3 months after the procedure, then gradually subsided. The patient currently leads a normal life using the upper right limb to the full extent without any restrictions (Figure 3).

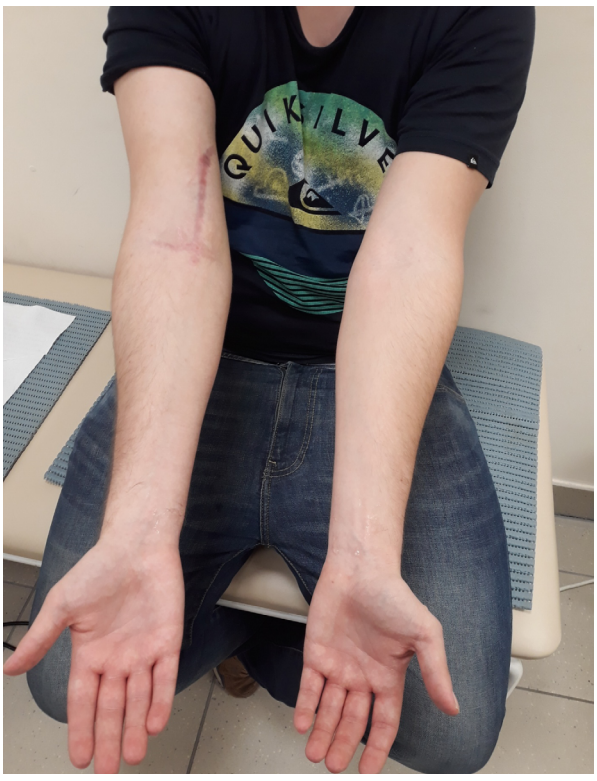

Fig. 3. Condition after last control visit

Discussion

Physical examination should be supported by ultrasound examination, oximetry or ABPI index testing. Currently, the best diagnostic tool is computed tomography with a contrast agent. Angiography is used to recognize trauma to smaller axial vessels located peripherally. However, the need for a delay in the event of an urgent surgery limits its use, above all to diagnostically difficult cases. There are often indications for arteriography during surgery.[5] First aid at the accident site is to control bleeding. This can be achieved by compressing the artery at the wound site and applying a pressure dressing. However, if limb bleeding persists, the cuff of the blood pressure monitor should be applied cardiacally from injury, pumping it to the appropriate level (200-250 mm Hg). Hemorrhage may lead to hypovolemic shock. It is important to implement the anti-shock procedure as early as possible. Access to the vein should be ensured, transfusions of blood replacers should be started, painkillers should be used, the patient should be positioned comfortably and the cover should be warm. A patient with probable vascular injury, in hypotension, with a systolic pressure <90 mmHg should be through a traumatic syndrome. The team should include: surgeon, interventional radiologist, orthopedic traumatologist, neurosurgeon and anesthesiologist. The patient should be provided with immediate access to the T-examination and operating room. For patients unstable in hypovolemic shock, one of the basic tools for ensuring circulatory stability is a resuscitative endovascular balloon occlusion of the aorta (REBOA), especially applicable to patients with chest and abdominal injuries. Antibiotic prophylaxis should always be considered before surgery and administration after surgery. Usually, classic methods of vessel reconstruction are used: primary suture, primary suture with venous or artificial patches, use of endogenous vein prostheses, artificial PTFE (Gore-Tex), Dacron. In exceptional circumstances - severe condition of the patient and with good collateral circulation, axial vessel ligation is possible. Recently, thanks to advances in endovascular surgery, stable patients can be treated using this surgical technique. It is often enough to close the small branches of the iliac arteries with the help of embolising materials: gelatin sponges, coil springs or surgical glues. Some arterial injuries can be treated by expanding the lumen of an endovascular prosthesis. In the case of dissections, the main goal is to supply the dissection gates, create conditions for clotting the false channel and directing blood to the proper channel. It seems that bare metal stents (BMS) and cobalt-chrome ones are best suited for this. Vessels exposed to external pressure are supplied with the help of nitinol self-expanding stents. Balloon expansion stents should be used in the initial sections of large vessels, where the accuracy of stent implantation is particularly important. Stent grafts are used in patients with interrupted arterial wall with possible passage through the guide wire in the lumen of the vessel. Stent grafts have also been used in the treatment of pseudo-aneurysms and post-traumatic arteriovenous fistulas.[2-6] With simultaneous artery damage and long bone fracture, management depends on the severity of ischemia. In case of severe limb ischemia, it may be necessary to undergo repair surgery before setting the bone

fracture. If the ischemia is minor, the fracture should be set first. In cases of multiple fractures, external stabilization seems to be the best solution. If the orthopedic surgery is prolonged and the blood supply to the limb worsens then a good solution is to place a temporary internal flow (shuntu) in the wounded artery.[7] The brachial artery is the most frequently damaged vessel in both peaceful and war conditions. It can be damaged if the shoulder and elbow are dislocated. Often, the brachial artery injury can be overlooked because the brachial plexus or its branch is damaged at the same time and then the symptoms of nerve damage are dominant. Good collateral circulation means that even a complete closure of the brachial artery may not lead to acute ischemia of the hand. Only the accumulation of blood under the fascia leads to the formation of the compartment syndrome (compartement syndrome), which results in ischemia and Volkmann's contracture. In order to treat the brachial artery injury, the arteries are usually exposed through a cut along the medial edge of the biceps or in the elbow pit. Remember not to damage the median nerve. The brachial artery after starting the stumps usually manages to end-to-end anastomosis, but sometimes it may be necessary to use a bridge. If the damage is widespread, blood flow should be brought even to the point of departure of the deep arm artery. Often, despite the restoration of circulation, simultaneous damage to the brachial plexus and shoulder-clavicular joint can cause a significant reduction in limb efficiency. With a large swelling of the forearm after surgery and the possibility of Volkman's contracture, the forearm fasciotoma must be remembered.[4-9] The surgeon's cooperation with the anesthesiologist is very important. The type of anesthesia affects the patient's condition and the operator's comfort of work. We have the option of general, local or local anesthesia. It seems that the type of anesthesia determines the type and severity of the injury itself and the general condition of the patient. While the patient's condition is good, i.e. it does not have general loads such as circulatory or renal failure, advanced respiratory failure and is not in shock, general anesthesia is the best type of anesthesia for extensive brachial artery injury. Local anesthesia is reserved for minor damage to the artery and the patient is in poor condition. Conduction anesthesia is possible provided no damage to the shoulder plexus has occurred. It is also important for the anaesthesiologist to take care of the patient's stable condition throughout the period of anesthesia and surgery, and in the postoperative period. Monitoring of pulse pressure, diuresis, fluid balance is one of the basic activities that must be performed in the intensive supervision room, where the patient should be found after the surgery.[10-16] It is also advisable to work closely with a neurologist to detect peripheral nerve damage early and respond appropriately to existing problems. In the case of bone or joint damage, an orthopedic surgeon will play an important role in the treatment process, as well as in a rehabilitator focused on starting the damaged limb as soon as possible.

Conclusion

Based on the above data, it should be concluded that in the case of extensive damage to vessels complicated by damage to bone, muscle and nerve structures, a syndrome is needed highly specialized professionals to obtain a beneficial effect of treatment. Often, however, typical symptoms can be masked by damage to other organs and the extent of the damage.

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LETTER TO THE EDITOR

Memory of Professor Antoni Leśniowski 1867–1940

Professor Antoni Lesniowski is one of the best-known Polish surgeons. As head of multiple Departments and Clinics in Warsaw he dedicated his career to broaden the knowledge and improve techniques used in the field of surgery, urology and ginecology. He presented a case of severe inflammation of the terminal ileum in 1903, 29 years before Burrill Bernard Crohn.

Professor Antoni Leśniowski was born on January 25, 1867 in Lebiedziowa, in the Lublin Province. He was the son of Karolina who's maiden name was Czarnocki and Peter, a veterinarian. He graduated from the Faculty of Medicine at the University of Warsaw in 1890. After a 2-year speciality training in Berlin, where he studied mainly in the field of urology, he returned to the Russian partition and from 1892, he worked as an assistant at the Second Department of Women's Surgery at the Baby Jesus Hospital in Warsaw. In 1912 he became the head of the surgery and urology department and the director of the Saint Anthony Hospital created by the Society for the Care of Poor Patients. From 1914 to 1919 he was the head of the Surgical and Urological Department of the Hospital of the Holy Spirit. He practiced surgery, urology and gynecology at the same time. Together, with his assistants, he tried to master the methods of urological examination, he worked on kidney function assessment methods. In 1915 he announced his own modifications of the migrating kidney operation. On June 1, 1919, Leśniowski was appointed a professor and head of the II Surgical Clinic of the University of Warsaw in the Hospital of the Holy Spirit and from July 1, 1920, head of the 1st Surgical Clinic at the Baby Jesus Hospital. In his later career he focused on gastrointestinal surgery, intestinal surgery and postoperative effects on the human body for example the acute acidosis.

He's the author of over 100 publications, including 28 urological ones, the translation of the german detailed textbook on surgery by C. Hueter and H. Lossen (1919), examination guidelines "*A diagram on examination of patients and writing hospital cards in a surgical clinic or surgery department*" (1930), the first Polish surgery handbook "*General surgery handbook*" (vol. I in 1923, vol. II in 1926, vol. III remained in manuscript) and many more in the field of surgery and ginecology.

Married to Wanda (maiden name Brajbisz), had a son Stefan, a neurologist, and two daughters - Jadwiga, a painter and Karolina, a philosopher.

In 1903, at a scientific meeting of the Warsaw Medical Society, he presented a specimen of the intestine (ileocecal region) cut out due to signs of intestinal obstruction, ulceration and inflammation. Accurate description of the dissected specimen and performed surgery by Leśniowski was published in the Memoirs of the Medical Society of Warsaw and the periodical *Medycyna*. On May 10, 1903, the Polish medical weekly *Medycyna* published an article entitled "*Contribution to bowel surgery*" by Professor Leśniowski from the Hospital Baby Jesus in Warsaw. The surgeon describes several cases of intestinal diseases in one of them, concluding that "*a chronic inflammatory process is taking place in the intestinal wall.*"

The same disease was described in 1932 by the American Burrill Bernard Crohn and since then in the world literature, not taking Leśniowski's priority, it is called Crohn's disease (only in Poland it is called Leśniowski - Crohn's disease). He also wrote a general surgery textbook.

Professor Antoni Leśniowski died on the 9th of April 1940 in Warsaw.

Professor Leśniowski is widely recognized as an authority in the field of surgery and gastroenterology. To honor his achievements, in Poland, the inflamatory bowel disease is recognized as Leśniowski-Crohn disease.

Michał Osuchowski
David Aebisher

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THE TITLE PAGE

The following information should be given on the **TITLE PAGE:**

- A complete title of the article (max 50 words), titles and subtitles should not be put into quotation marks and ended with a full stop.
- Abbreviated title of the article (*Running Head*).
- Names, last names of the Authors (without degrees and titles).
- Affiliations and participation of all of the Authors (according to a pattern below**).
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- The title page should also give information about a source of funding the research (grants, donations, subventions etc.) and conflict of interest.

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A. Author of the concept and objectives of paper
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Example:
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1. The Institute of Physiotherapy, University of Rzeszow, Poland
2. Centre for Innovative Research in Medical and Natural Sciences', Medical Faculty of University of Rzeszow, Poland

The **MAIN BODY** of the manuscript should contain:

- A full title of the article.
- 3–6 keywords, chosen in compliance with the MeSH system (Medical Subject Headings Index Medicus http://www.nlm.nih.gov/mesh/MBrowser.html). Keywords cannot be a repetition of the title. Give a list of Abbreviations in alphabetical order.
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ARRANGEMENT OF TEXT

An original article should contain the following elements:

- Introduction
- Aim of the study
- Material and methods
- Results (used statistical methods should be described in detail in order to allow for verifying the results)
- Discussion
- Conclusion
- References

Case study should contain the following elements:

- Introduction
- Case description
- Discussion
- A summary
- References

Systematic review should contain the following elements:

- Introduction
- Description of the subject literature (a source of publication, data range)
- Analysis of the literature
- A summary
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Review article should contain the following elements:

- Introduction
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- References

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Examples:

- The degree of respiratory muscles fatigue depends on the applied exercise protocol and the research group's fitness level. [1, 2] The greatest load with which a patient continues breathing for at least one minute is a measure of inspiratory muscles strength.[3]
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Article from a journal, number of authors more than 6	Gonzalez ME, Martin EE, Anwar T, et al. Mesenchymal stem cell-induced DDR2 mediates stromal-breast cancer interactions and metastasis growth. Cell Rep. 2017;18:1215-28. Jordan J, Toplak H, Grassi G, et al.Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and heart failure. J Hypertens. 2016;34:1678-88.
Article from an online journal	Coppinger T, Jeanes YM, Hardwick J, Reeves S. Body mass, frequency of eating and breakfast consumption in 9-13-year-olds. J Hum Nutr Diet. 2012;25:43-9. doi: 10.1111/j.1365-277X.2011.01184.x. Cogulu O, Schoumans J, Toruner G, Demkow U, Karaca E, Durmaz AA. Laboratory Genetic Testing in Clinical Practice 2016. Biomed Res Int. 2017;2017:5798714. doi: 10.1155/2017/5798714.
Websites	Cholera in Haiti. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/haiti-cholera/. Published October 22, 2010. Updated January 9, 2012. Accessed February 1, 2012. Address double burden of malnutrition: WHO. World Health Organization site. http://www.searo.who.int/mediacentre/releases/2016/1636/en/. Accessed February 2, 2017.
Book	Naish J, Syndercombe Court D. Medical Sciences. 2nd ed. London, Elsevier;2015. Modlin J, Jenkins P. Decision Analysis in Planning for a Polio Outbreak in the United States. San Francisco, CA:Pediatric Academic Societies;2004.
Chapter in a book	Pignone M, Salazar R. Disease Prevention & Health Promotion. In: Papadakis MA, McPhee S, ed. Current Medical Diagnosis & Treatment. 54th ed. New York, NY: McGraw-Hill Education; 2015:1-19. Solensky R. Drugallergy: desensitization and Treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. Allergens and Allergen Immunotherapy. 3rd ed. New York, NY: Marcel Dekker; 2004:585-606.

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