FUNCTIONS OF A NEUROMUSCULAR CENTRE

NALOGE CENTRA ZA ŽIVČNOMIŠIČNE BOLEZNI

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Abstract – *Main functions of a neuromuscular (NM) centre are making diagnosis, treatment and counselling. Some other functions, e. g. forming a register and epidemiological endeavours, could be added. All these activities are expected to be achieved by multidisciplinary approach with the idea that members use the same guidelines and share the same knowledge.*

NM diseases affect lower levels of the nervous system that is motor units (motor cells in the brainstem and spinal cord, nerve roots, cranial and peripheral nerves, neuromuscular junction, and muscles). There are many such diseases; a few are more common others are rare.

Rational approach in making a diagnosis can be divided into several steps. The process begins with a person with clinical symptoms and signs which raise the suspicion of NM disease. The first step is the description of the predominant pattern of muscular wasting and weakness (e. g. limb-girdle, distal, ocular, facio-scapulo-humeral). Each of these syndromes require a differential diagnosis within the motor unit territory what is achieved by means of EMG and muscle biopsy. The latter is even more important to define the nature of the abnormality. Disease nature can also be determined biochemically and, as NM disorders are commonly genetically determined, at the molecular genetic level. Treatment modalities include drugs (causative and symptomatic) and other measures such as promoting and maintaining good general health, preventing skeletal deformities, physiotherapy, orthoses, surgery, and prevention of respiratory and cardiac functions. Counselling is mainly by social workers that focus on the practical aspects of coping with illness and disability and by genetic counsellors who gave advise on family planning.

Ključne besede: *center za živčnomišične bolezni; diagnosticiranje; zdravljenje; svetovanje*

Izvleček – *Glavne naloge centra za živčnomišične bolezni so diagnosticiranje, zdravljenje in svetovanje. Med ostalimi pomembnimi nalogami lahko omenimo vodenje registra in epidemiološke študije. Vse omenjene aktivnosti so plod multidisciplinarnega dela. Ideja takšnega dela je, da člani timov na osnovi skupaj pridobljenega znanja uporabljajo ista načela dela.*

Živčnomišične bolezni prizadenejo nižje nivoje živčevja, točneje motorično enoto. Le-ta obsega motorične živčne celice možganskega debla in hrbtenjače, živčne korenine, možganske in periferne živce, živčnomišični stik in mišice. Med številnimi različnimi živčnomišičnimi boleznimi so le redke pogostejše, večino od njih pa srečamo poredko ali celo izjemno redko. Postavitev specifične diagnoze ima, kljub temu da za večino teh bolezni ni vzročnega zdravljenja, prognostični pomen in je osnova za genetsko svetovanje. Proces diagnosticiranja lahko smotrno razdelimo v več zaporednih faz. Začetek je vedno vezan na bolnika s simptomi in znaki, sumljivimi za živčnomišično bolezen. Najprej je v diagnostičnem postopku potrebno definirati vzorec mišičnih atrofij in šibkosti. Vsak od vzorcev (npr. proksimalna ali distalna prizadetost udov, očesna prizadetost, facioskapulohumeralna prizadetost) zahteva premislek glede lokacije okvare v motorični enoti. Pri tem se opremo na elektromiografske in morfološke (mišična biopsija) laboratorijske preiskave. Ugotoviti je potrebno tudi morebitno prizadetost drugih organov (npr. siva mrena pri miotonični distrofiji, prizadetost očesne mrežnice pri mitohondrijskih boleznih). Morfološke preiskave pa so pomembnejše za ugotovitev vzroka bolezni. Vzrok je definiran na morfološkem, biokemičnem ali, ker gre pogosto za podedovane bolezni, na molekularnogenetskem nivoju.

Zelo pogosto so živčnomišične bolezni gensko pogojene. To pomeni, da so njihov vzrok spremembe v genih, ki jih imenujemo mutacije. Geni so v bistvu recepti ali navodila za sestavo različnih telesnih beljakovin. V primeru genskih mutacij določenih beljakovin lahko ni ali pa je njihovo delovanje spremenjeno. Načini dedovanja pri človeku so različni: avtosomno dominantno, avtosomno recesivno, vezano na kromosom X in mitohondrijsko.

Načini zdravljenja obsegajo zdravljenje z zdravili (vzročno in simptomatsko) ter druge ukrepe za vzdrževanje dobrega splošnega stanja, preprečevanje skeletnih nenormalnosti, fizioterapijo, ortopedske pripomočke, operativno zdravljenje ter preprečevanje oz. odgoditev motenj dihanja in srčnih funkcij. Med zdravila, s katerimi nekatere živčnomišične bolezni lahko pozdravimo, sodijo kortikosteroidi in druga zdravila, ki zavirajo imunske reakcije. Z njimi zdravimo npr. vnetne bolezni mišic in živcev ter miastenijo gravis. Proti vzroku nastanka bolezni naj bi bilo usmerjeno tudi delovanje zdravi-

la riluzol, ki lajša simptome in znake amiotrofične lateralne skleroze. Zdravljenje dednih bolezni bi bilo v načelu mogoče z zamenjavo bolezensko spremenjenih genov z zdravimi. Razvoj moderne znanosti zbuja upanje, da bo to nekoč mogoče.
Svetovanje je večinoma v rokah socialnih delavcev (praktični nasveti za premagovanje težav v zvezi z boleznijo) in genetskih svetovalcev (v zvezi z načrtovanjem družine).
Epidemiološke študije so osnova za spoznavanje naravnega poteka in klinične slike bolezni, ugotavljanje nevarnostnih dejavnikov, prepoznavo največjih problemov javnega zdravstva in ovrednotenje učinkovitosti zdravstvenih ukrepov. Rezultati teh študij so uporabni za preučevanje razprostranjenosti bolezensko spremenjenih genov, za načrtovanje medicinske, socialne in ekonomske pomoči bolnikom in kot pomoč prakticirajočemu nevrologu pri prepoznavi prizadetih družin.
V skupinah strokovnjakov, ki se ukvarjajo z bolniki, ki imajo živčnomišične bolezni, sodelujejo nevrologi, nevropediatri, nevrofiziologi, nevropatologi, genetiki, fiziatri, ortopedi, kardiologi, otorinolaringologi, pulmologi, biokemiki, molekularni genetiki, socialni delavci, fizioterapevti, medicinske sestre, delovni terapevti in drugi.

Introduction

The following is an attempt to describe main functions of a neuromuscular (NM) centre. It is partially based on our own experience. Our Neuromuscular Unit was established almost exactly 30 years ago. In a way it was much easier to work in this field at that time since distinct diagnostic categories were much fewer. But, on the other hand, it was necessary during this pioneering period to set up several different activities indispensable for its functioning. Firstly, histologic and electrophysiologic diagnostic tests were developed in parallel with increased clinical experience. Physical therapy and other treatment modalities were provided to newly classified neuromuscular patients as well as genetic counselling. Also from the very beginning the orthopaedic surgeon, physiatrist, and social worker, were added to the team. The Register of the Slovene Neuromuscular patients was started. The drawback of our relatively small Unit (the limitation is set by smallness of our country) is that we see only a limited number of patients and can thus get rather limited experience in the field. Neuromuscular disease categories are namely exceedingly numerous and at the same time most of them very or extremely rare.
Generally, main functions of a neuromuscular centre would be making diagnosis, treatment and counselling but some other functions have also to be mentioned.

Making a diagnosis

NM diseases affect lower levels of the nervous system that is the so called motor unit or the dorsal root ganglion neurone, and include disorders of motor cells in the brainstem and spinal cord, nerve roots, cranial and peripheral nerves, neuromuscular junction, and muscles. There are many diseases of nerve and muscle; a few are common, many are rare or even extremely rare. Some of them are amenable to the causative treatment but the majority are not and could be approached only by managing the disease symptoms. Neurologists are therefore often in doubt how extensively to investigate their patients. Such endeavours, nowadays largely based on molecular diagnostic techniques, are sometimes thought to be of only academic interest. Here we would like to emphasise that making specific diagnosis is not only of theoretical importance. It sometimes means that specific treatment can be initiated, definitely helps in making prognosis (future plans), and is essential for genetic counselling.
Rational approach in making a diagnosis can be divided into several steps that are in principle to be followed one after another (Bulcke and Baert 1982). The process begins with a person with clinical symptoms and signs which raise the suspicion of NM disease (Mastaglia and Laing 1996). This may be a baby with paucity of movements, and with breathing and feeding difficulties or a child that does not perform well in gym classes and sports. Symptoms in adulthood include difficulties with running, walking or manipulation of objects, painful muscle spasms, breathing, tiredness and fatigue, intolerance to exercise, muscular pain, tenderness, stiffness, alterations in muscle mass, spontaneous muscle activity, sensory disturbances, and others.
The very basic step is the description of the predominant pattern of muscular wasting and weakness, the two signs that are nearly obligatory for the diagnosis. The weakness syndrome in NM diseases typically differs from that in central nervous system diseases. Most commonly it affects proximal (limb girdle weakness) or distal limb muscles (distal weakness) but may also have more specific distributions, eg. ocular, oculopharyingeal, and facio-scapulo-humeral. Why most NM diseases, regardless of their anatomical localisation within the motor unit, follow one or the other pattern, is poorly understood. Pattern on itself is however not diagnostic. Each of the syndromes require a differential diagnosis within the motor unit territory. This demands careful, analytical and often multidisciplinary examination of all muscles: muscle strength testing by Medical research Council Scale, functional testing, muscle imaging, examination of the pulmonary, laryngeal, pharyngeal and oesophageal functions, and heart examinations. Muscle imaging (MRI, CT, ultrasound) can also be used to guide which muscle and where to biopsy.
Next to be searched for is whether any other organ is involved. Muscle illness may be only one of the phenotypical disease characteristics. Examples are slit-lamp examination to detect cataract in myotonic dystrophy, electrophysilogical studies to find retinal affection in mytochondrial diseases, and biochemical studies to rule out endocrine dysfunctions in these diseases. Such analyses allow description of complete disease phenotype and sometimes suffices to make a diagnosis.

Further diagnostic procedures relay on laboratory examinations. First it is necessary to determine localisation of the abnormality in the motor unit (motor cells in the spinal cord, nerves, neuromuscular junction, muscle tissue) by EMG and/or muscle biopsy. Diseases that affect these components differ and are designated as neuronopathies, neuropathies, neuromuscular junction disorders and myoptahies. Specific EMG patterns rather accurately pinpoint that localisation. The same is true also for muscle biopsy; muscle fibre type grouping is typical for neurogenic disorder while eg. considerable variations in fibre diameters and central locations of nuclei characterise myopathy.
Muscle biopsy, however, more specifically serves to define the nature of the abnormality, especially in myopathies. Nature of the disease may be defined at different levels: morphologically (e. g. inflammation, structural and immunohistochemical abnormalities), biochemically, or, as it is nowadays in case of inherited disorders nearly mandatory, at the molecular genetic level.

Genetic disorders

Quite commonly NM disorders are genetically determined; that means they are caused by changes, named mutations, in genes (Reilly and Hanna 2002). Genes, stored on strands called chromosomes, are basically composed of DNA (deoxyribonucleic acid) and serve as recipes or instructions for the production of many thousands of different bodily proteins. Proteins function as building blocks of tissue cells but also carry out their functions as e. g. sending and receiving signals, breaking down large molecules, synthesising new molecules from smaller ones, and production of energy. In case of disease-causing mutations particular proteins are either absent or altered in their function to the different extents. Effects of mutation for a human depend on many factors, among others also on how crucial the protein is in the body. Proteins involved in NM disorders are normally present in nerve or muscle cells. Muscle proteins, when altered, may e. g. cause malfunction of muscle contraction, the way in which the muscle cells receives signals from nerve cells, or disruption of its membrane integrity which is normally protective against the workload.
The other important characteristic of genetic diseases is their predictable transmission from one generation to another. The mode of transmission can be either autosomal or sex chromosome linked (dominant or recessive) or coupled to mitochondrial DNA. To understand heredity basic knowledge on chromosomes is required. Humans have 23 pairs of chromosomes, one from each of their parents. They are located in cell's nucleus. Some of the DNA is stored also in mitochondria. Twenty-two pairs of chromosomes are identical (autosomal chromosomes), while the 23rd pair differs according to gender (2 X chromosomes in females and X and Y chromosomes in males – sex chromosomes). Autosomal dominant conditions disclose themselves when only one of the gene pairs is mutated while autosomal recessive conditions require mutations in both. In the former the chance of having an affected child is 50% while in the latter 25% with each conception. X-linked disorders come from mutations in genes on the chromosome X. Males are in this case generally more or exclusively affected compared to females. The female namely has the second X chromosome with normal gene that may compensate for the mutated one. Female carriers have greater chance of having an affected child (50% for each male) than the affected males (normal sons, 50% chance for girls to be carriers). The additional genes, which make up less than 1% of a cell's DNA, reside in circular chromosomes inside mitochondria. Their mutations cause the so called mitochondrial diseases which follow different rules of inheritance. Mothers can pass on mitochondrial mutations to their children, but fathers can't. Quite often, a genetic disease occurs in a family when no one else has been known to have it. This may happen in case of recessive inheritance, in X-linked disorders (male child of a female carrier) but commonly also as a result of new mutations.
Clinicians should, as the first step, in order to unravel the genetic nature of the disease, construct family tree and examine other family members.

Treatment

After making a diagnosis treatment is to be considered. Use of drugs is most commonly perceived as the cornerstone measure though it may also be risky (Ringel 1987). Despite that patients who do not receive a prescription after visiting a doctor may feel disappointed. Sometimes it is possible to apply drugs that can cure NM diseases as e. g. in case of inflammatory afflictions. But most commonly treatment is only symptomatic. As a cure corticosteroids and immunosuppressive medications, and high doses of immunoglubulines may be applied. They are used to treat myasthenia gravis and inflammatory myopathies and neuropathies. Because of many potential side effects from long-term administration of these drugs it is important to individualise and carefully monitor such therapy. Among other agents which action may be directed against the disease cause it worth to mention riluzol, the drug used in treating patients with amyotrophic lateral sclerosis. A cure for muscular dystrophy and other genetically determined diseases would mean replacing the defective causative mutated gene by normal one. New technological developments raise hopes that this possibility, the so called gene therapy might become possible in the near future. Examples of symptomatic treatment may be respiratory drugs, pain relief (including treatment of muscle cramps), amelioration of constipation, anxiety, depression, insomnia, and medications that reduce swelling of legs.
Even when there is no cure available, a great deal can be done to relive many of the problems associated with NM diseases and to improve the quality of life. Such approach is based on promoting and maintaining of good general health, preventing of skeletal deformities through exercises, physiotherapy, orthoses, and surgery and prevention of respiratory and cardiac functions.

Counselling

Social workers mainly focus on the practical aspects of coping with illness and disability, such as insurance reimbursement issues and other financial problems, equipment and housing needs, transportation and home care. They can also deal with psychosocial issues raised by disability.
Genetic counselling consists of explaining the couple the facts that can guide them in making decisions on their offspring (Emery 2000). The information include diagnostic data, course and likely outcome of the disease, and mode of inheritance. The counsellor should be aware that his perceptions of the disease and its risks may not be the same as parents'.

Epidemiology

Effective public health actions are based on scientifically derived information about factors influencing health and disease. The basic sciences of public health are epidemiology and biostatistics. Epidemiological studies are common activities of teams associated with neuromuscular centres and are used to describe the distribution, dynamics and determinants of disease and health in human populations (Detels et al. 2002). Its applications in public health and medicine include: establish-

ing the natural history and clinical picture of a disease, identifying the disease risk factors, identifying the major public health problems in a community, and evaluating the effectiveness of intervention programmes. Epidemiological data related to neuromuscular diseases may have several more specific purposes. They can be used to study certain genetic parameters (e. g. frequency of different gene occurrences), to monitor preventive measures by genetic counselling, planning medical, social, and economic help, and to assist practising neurologist in identifying affected families.

Interdisciplinary approach

Interdisciplinary approach in managing patients is most desired. Its idea is that members (neurologist, neuropaediatrician, neurophysiologist, neuropathologist, geneticist, phyisiatrist, orthopaedic surgeon, cardiologist, ENT specialist, pulmologist, biochemist, molecular geneticist, social worker, physiotherapist, nurse, occupational therapist...) use the same guidelines and share the same knowledge.

As mentioned NM patients encounter a variety of medical professionals in their contacts with health care system. Most NM units are directed by neurologists, physicians that specialise in the nervous system and muscle diseases. There main interest is in diagnosis and drug treatment but may be experienced in other aspects of dealing with patients. Physiatrists or rehabilitation doctors help people to cope the physical aspects of a disorder (e. g. moving, eating). Cardiologist treat heart problems if and when they arise (some forms of muscular dystrophy, Friedreich's ataxia). Pulmologists, doctors that specialise in diseases of lungs and the associated structures, are involved as NM diseases may also affect muscles that control breathing. These has been increasingly recognised as one of the most important aspects of treatment. Orthopaedists are concerned with bones and joints and their associated structures, such as muscles and tendons. Bones and joints are in NM diseases affected secondarily, due to the prolonged muscle weakness. Joints may become fixed in certain position and could be released only by surgery. The spine can also be affected by abnormal curvatures (scoliosis). These very debilitating condition may also need surgical correction. Severe disability can often result in psychological distress what sometimes results in a need for psychiatric or psychological interventions. Primary care physicians or family doctors that take care of the person as a whole, are important part of the team. Many health professionals who are crucial in providing support for the patients are not medical doctors. They include physical and occupational therapists, respiratory therapists, speech-language pathologits, dietitians and nutritionists, nurses, social workers, and genetic counsellors.

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