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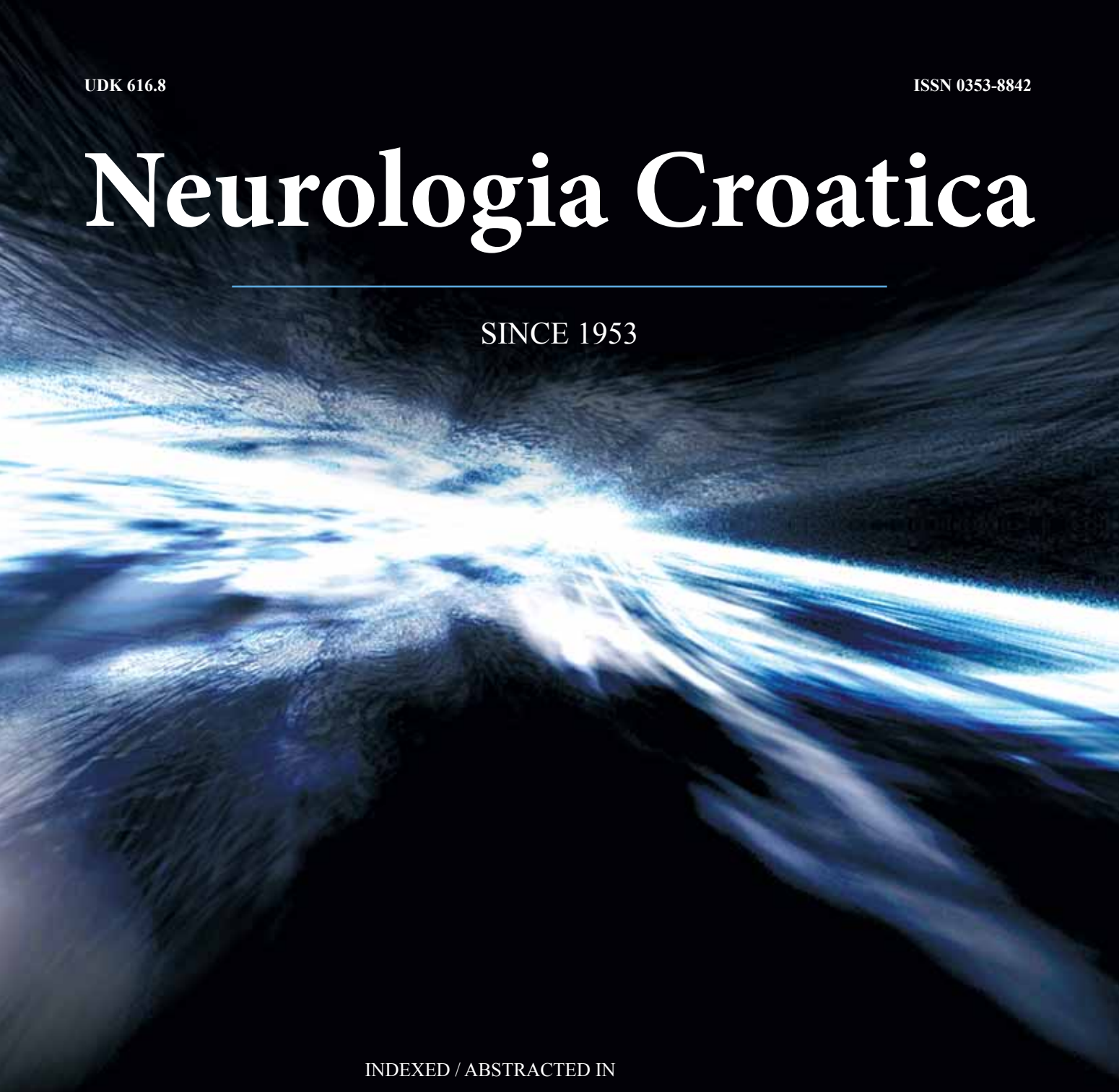

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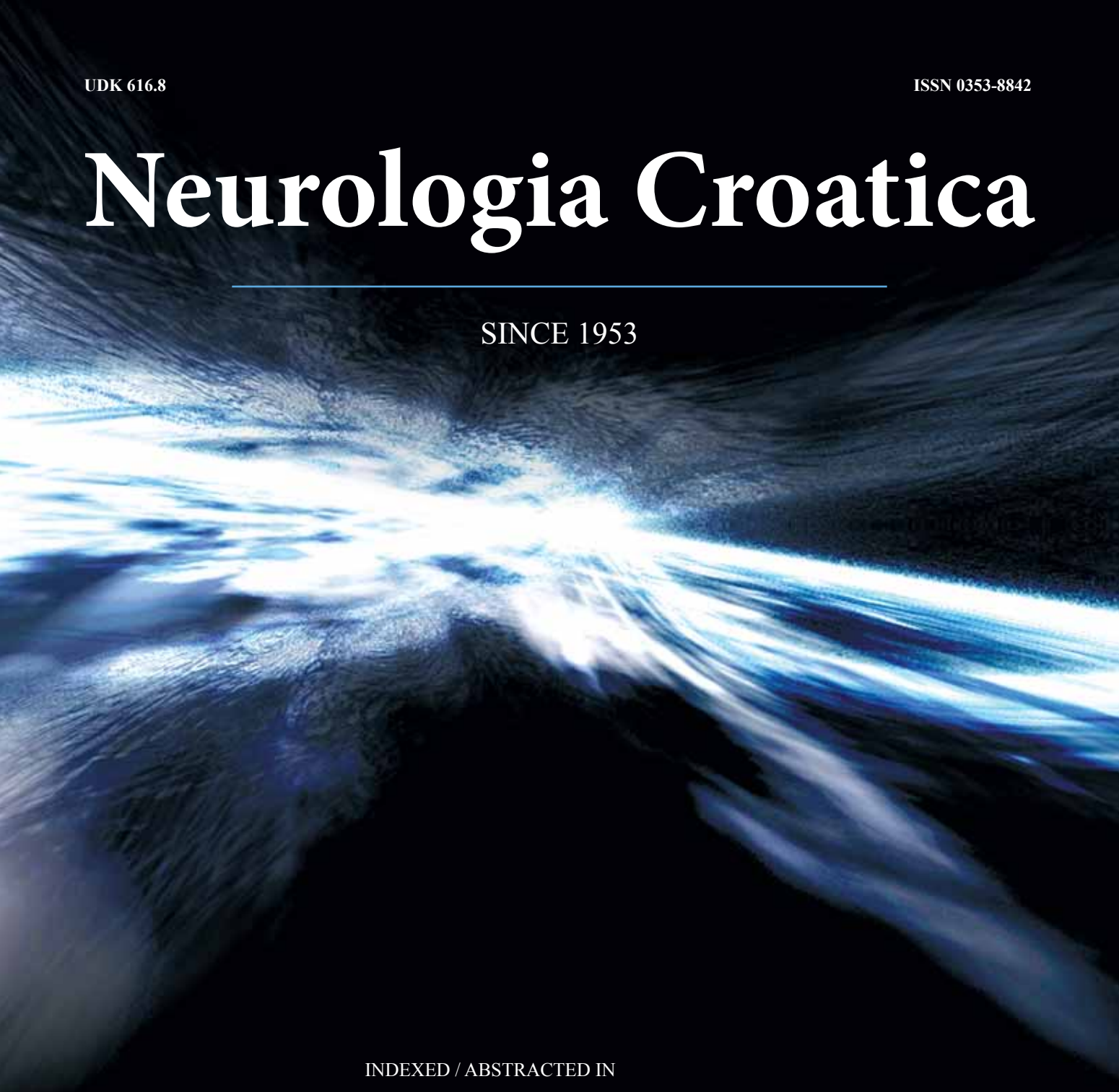

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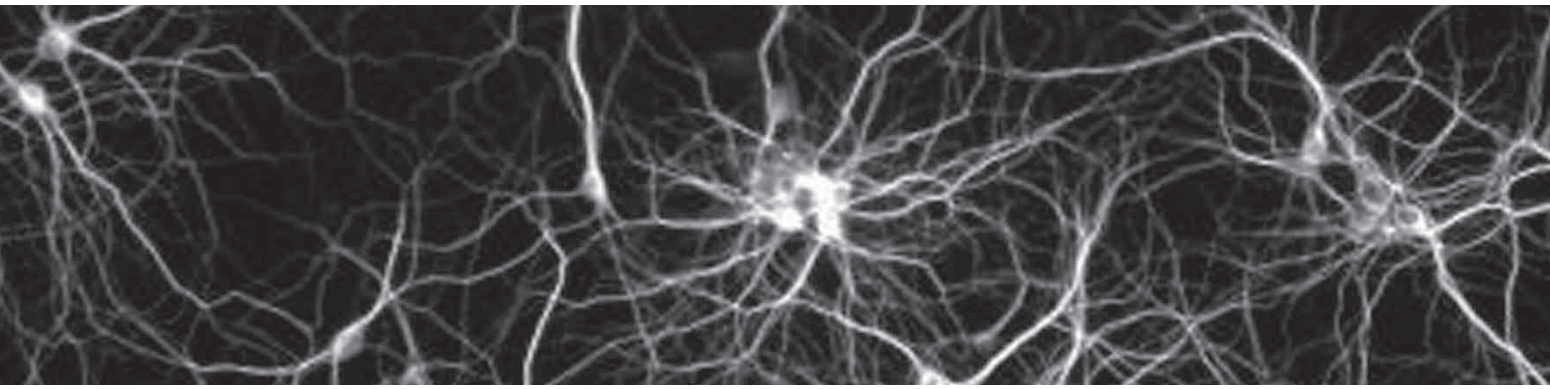


Editorial

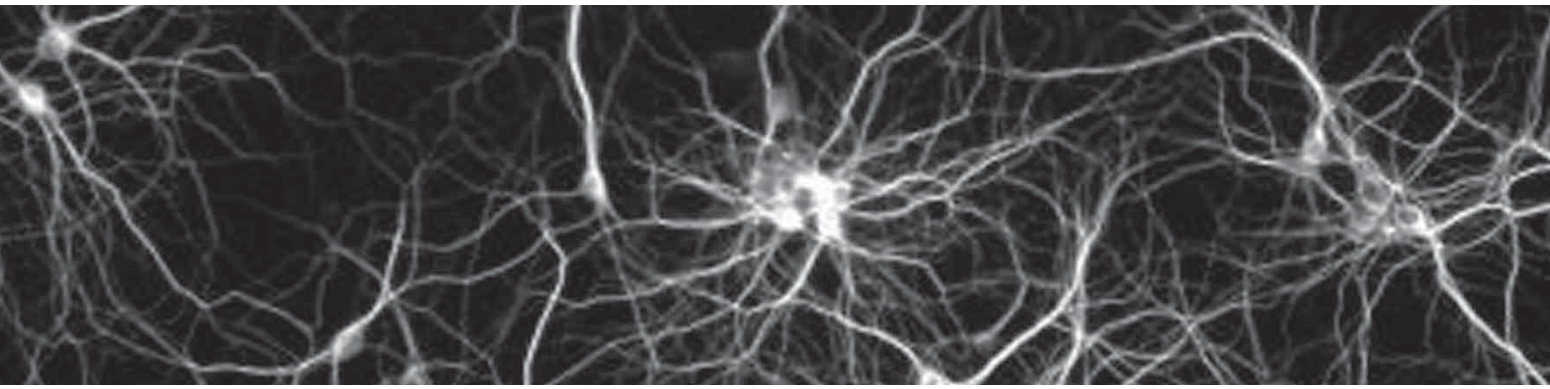
Dear readers and colleagues,

Welcome to the first issue of Neurologia Croatica 2015. I hope that you will enjoy reading it and that we will continue increasing national and international scientific popularity of our journal. In the first part of this issue, we bring two interesting clinical reviews, which are in my opinion educative especially for younger colleagues. One review is dedicated to the new diagnostic criteria for Alzheimer's disease which perceive this clinical entity as a continuum that encompasses three different stages: preclinical phase, symptomatic pre-dementia phase (mild cognitive impairment) and dementia phase. These criteria also place emphasis on using biomarkers to provide earlier and more specific diagnosis in order to ensure effective treatment. Another review brings data on small fiber neuropathy, a relatively common but underdiagnosed and undertreated disorder, given that clinical picture can be difficult to interpret. It is associated with various systemic diseases. However, there are most recent discoveries of several novel mutations to sodium channels in patients with idiopathic type. The diagnosis of this clinical entity relies on clinical features (painful paresthesias and/or signs of autonomic dysfunction) combined with abnormal quantification of intraepidermal nerve fiber density and/or deficit in temperature threshold on quantitative sensory testing. Early diagnosis is crucial because it can lead to prompt initiation of causative or symptomatic treatment.

The second part of this issue brings two interesting case reports – one is the second reported case of chordoid meningeoma situated in the third ventricle in a pediatric patient, with good clinical outcome after second operation due to tumor relapse. Another case report published by colleagues from Taiwan discusses clinical entity of the pontine Ménière's syndrome that might be a variation of pontine transient ischemic attack with caudal pontine tegmentum syndrome or a pathophysiology similar to that of vestibular migraine.

We are grateful to all reviewers of the articles published in this issue for their scientific and professional expertise. At the end, I invite you to submit your papers to the journal Neurologia Croatica. Your contribution to the quality of this journal will be highly appreciated.

Assist. Prof. Željka Petelin Gadže, M.D., Ph.D.
Assistant Editor



New diagnostic criteria for Alzheimer's disease

Marija Vukšić, Nataša Klepac[1]

ABSTRACT – The goals of this review were to investigate the previously published criteria for the diagnosis of Alzheimer's dementia which are used in clinical practice. Today, we are able to explore environmental factors and genetic predisposition for developing Alzheimer's dementia, to detect biomarkers in cerebrospinal fluid, to find neuroimaging characteristics of the disease, and eventually to notice a number of clinical manifestations of the pre-dementia and dementia phase. The criteria for the diagnosis of probable Alzheimer's dementia have been based on the National Institute on Aging and the Alzheimer's Association (NIA-AA) diagnostic criteria from 2011 and The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria from 2013, and they appear to have similar accuracy in clinical practice. Further research is needed to define more specific and sensitive diagnostic criteria and more effective treatment.

Key words: Alzheimer's disease, diagnostic criteria, biomarkers

INTRODUCTION

Alzheimer's disease (AD) is the most common form of neurodegenerative dementia, accounting for 50-60 percent of cases (1). Dementia is a disorder characterized by a decline in cognition involving one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) (2). Age remains the strongest risk factor for dementia, particularly for AD. The incidence of AD approximately doubles every 10 years after the age of 60 (3). The challenge and yet perhaps the greatest promise in effectively treating neurodegenerative disease lies in prompt diagnosing. The reality is that the pathophysiological process begins more than a decade prior to the stage of clinically detectable symptoms (4).

Regarding diagnosis, the clinical criteria established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) (5) have been revised by the National Institute on Aging and the

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Alzheimer Association (NIA-AA) (6, 7). These criteria for AD incorporate two notable differences. First, the AD process is considered as a continuum that encompasses three different disease stages: 1) preclinical phase, in which subjects are cognitively normal but have AD pathology; 2) symptomatic pre-dementia phase: mild cognitive impairment (MCI); and 3) dementia phase: AD (6). The original 1984 clinical criteria for AD defined it as having a single stage, dementia, while the diagnosis relied solely on clinical symptoms. It assumed that people free from dementia symptoms were disease-free. Diagnosis was confirmed only on autopsy, when the hallmarks of the disease, i.e. abnormal amounts of amyloid proteins forming plaques and tau proteins forming tangles, were found in the brain. Since then, research has determined that AD may cause changes in the brain a decade or more before the symptoms appear and that symptoms do not always directly relate to abnormal changes in the brain caused by AD. For example, some elderly people are found to have abnormal levels of amyloid plaques in the brain on autopsy, yet having never shown signs of dementia during life. It also appears that amyloid deposits begin early in the disease process but that tangle formation and loss of neurons occur later and may accelerate just before the clinical symptoms appear (6,8).

In this review, we provide an overview of current diagnostic criteria for Alzheimer's dementia including preclinical phase, available biomarkers and clinical features.

BIOMARKERS OF ALZHEIMER'S DEMENTIA (in preclinical phase)

Preclinical AD refers to the stage of AD in which the molecular pathology is already present in the brain but is not yet clinically expressed (9). Neuropathologically, it is characterized by amyloid plaques, tau containing neurofibrillary tangles, activated microglia around amyloid plaques, and amyloid angiopathy and microhemorrhages in some individuals with AD (10).

The genetic basis of AD is best understood in the early-onset form, which accounts for less than one percent of cases and typically follows an autosomal dominant inheritance pattern related to mutations in the genes that alter amyloid-beta (Aβ) protein production, aggregation, or clearance. The genetic basis of late-onset AD (sporadic AD) is more complex, with susceptibility likely conferred by a variety of more common but less penetrant genetic factors, such as apolipoprotein E (*APOE*) alleles. Those genetic factors are interacting with many environmental and epigenetic influences such as age, hypertension, hypercholesterolemia, diabetes, tobacco smoking, obesity, lifestyle, social, mental and physical activity, level of education and cognitive reserve, head trauma, obesity, high alcohol consumption, depression, etc.

Newer criteria place emphasis on using biomarkers to provide an earlier and more specific diagnosis (8).

Structural imaging (CT or MRI)

In AD, the typical imaging appearance is global brain atrophy with early disproportionate symmetric involvement of medial temporal lobe structures including the hippocampi (11). It can differentiate AD from aging and from dementia with Lewy bodies (DLB) and vascular cognitive impairment (12, 13). Medial temporal lobe atrophy can predict which individuals will develop clinical AD from MCI state (12, 14). Progressive atrophy of the parietal/occipital lobes is supportive of AD and in particular in distinguishing AD from frontotemporal dementia (FTD); incorporating visual ratings of posterior atrophy can improve distinction of AD from other causes of dementia (11). Rates of whole brain and hippocampal atrophy, calculated from serial volumetric MRI are sensitive markers of progression of neurodegeneration and are increasingly used as outcome measures in trials of potentially disease modifying therapies in AD (14).

Functional imaging (PET, SPECT, fMRI, amyloid PET tracers)

Functional brain imaging with 18F-fludeoxyglucose positron emission tomography (FDG-PET), functional MRI (fMRI), perfusion MRI or *single-photon emission computerized tomography (SPECT)* reveals distinct regions of low metabolism (PET) and hypoperfusion (SPECT, fMRI) in AD. These areas include the hippocampus, the precuneus (mesial parietal lobes), and the lateral parietal and posterior temporal cortex (15-21). Amyloid PET tracers (F18-florbetapir, F18-flutemetamol, F18-florbetaben) that measure amyloid lesions in the brain have been developed as tools to aid in the diagnosis of AD *in vivo*, aid in prognosis, speed development of anti-amyloid drugs and differentiating AD from other causes of dementia (22-24). Currently, the availability and cost of amyloid PET imaging still limit its use in clinical practice (25).

Cerebrospinal fluid's biomarkers (β-Amyloid, Tau, Phospho-tau 181)

The CSF levels of Aβ1-42, thought to be one of the key pathological forms of Aβ in brain tissue, are reduced in AD, with the degree of reduction correlating with the brain amyloid plaque load (26). Reduction of CSF Aβ1-42 occurs years before symptom onset (27), and has good positive predictive value for conversion from MCI to clinical AD (28); accordingly, CSF Aβ1-42 is now included in the new diagnostic criteria for MCI due to AD (7). In clinical practice, normal CSF Aβ1-42 in a demented individual should prompt re-evaluation of the AD diagnosis. Other forms of β-amyloid, notably Aβ1-40, can be measured in CSF and may better reflect both total brain Aβ burden than Aβ1-42 (29) and may improve differential diagnosis in certain circumstances (30, 31), but this has not yet entered routine clinical practice.

The CSF levels of t-tau and tau phosphorylated at 181 (p-tau) are both increased in AD. T-tau is increased after stroke, in inflammatory conditions and in other neurodegenerative diseases, most notably in Creutzfeldt-Jakob disease, where the levels are often in the orders of magnitude higher than in AD; p-tau elevation is thought to have high specificity for AD (32). Stability and reproducibility of t-tau and p-tau levels are good, and the levels remain stable over periods of up to 6 months (33), suggesting that these biomarkers may be capable of detecting small biochemical changes induced by treatment.

Several studies have demonstrated that the combination of low CSF Aβ1-42 and elevated t-tau and p-tau could distinguish individuals with MCI/incipient AD from those without it with 95% sensitivity and 87% specificity (34). On the research basis, the combination of low Aβ42, elevated tau and p-tau has also been used to predict future cognitive decline in healthy older individuals (35). In clinical practice, the combination of low CSF Aβ1-42 and elevated tau (or p-tau) to Aβ1-42 ratio is often used to support the diagnosis of AD, with one recent study suggesting the tau:Aβ42 ratio to be the most robust single biomarker combination (36).

CLINICAL FEATURES

Symptomatic pre-dementia phase: mild cognitive impairment

The MCI stage is marked by symptoms of memory problems, enough to be noticed and measured, but not compromising the person's independence. People with MCI may or may not progress to Alzheimer's dementia (6-8, 37).

There should be evidence for lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. Impairment in episodic memory (i.e. the ability to learn and retain new information) is seen most commonly in MCI patients who subsequently progress to the diagnosis of AD. Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors on performing such activities than in the past. Nevertheless, they generally maintain their independence of their daily life functioning, with minimal aid or assistance. These cognitive changes should be so mild as to show no evidence of significant impairment in social or occupational functioning. The person should not meet the criteria for dementia (37).

Dementia phase: Alzheimer's disease

Memory impairment is an essential feature of AD and is often its earliest manifestation. Declarative memory for facts and events, which depend on mesial temporal and neocortical structures, are profoundly affected in AD, while subcortical systems supporting procedural memory and motor learning are relatively spared until quite late in the disease. A subset of declarative memory, that of specific events and contexts (episodic memory) is more profoundly impaired in early AD, compared with memory for facts such as vocabulary and concepts (semantic memory), which often becomes impaired somewhat later. Semantic memory is encoded in neocortical (nonmesial) temporal regions. Within episodic memory, there is a distinction between immediate recall (e.g., mental rehearsal of a phone number), memory for recent events (which comes into play once material that has departed from consciousness must be recalled), and memory of more distant events. Memory for recent events, served by the hippocampus, entorhinal cortex, and related structures in the mesial temporal lobe, is prominently impaired in early AD (15, 38, 39). In contrast, immediate memory (encoded in the sensory association and prefrontal cortices) is spared early on, as are memories that

are consolidated for long periods of time (years), which can be recalled without hippocampal function. Memory deficits develop insidiously and progress slowly over time, evolving to include deficits of semantic memory and immediate recall. Impairments of procedural memory appear only in late stages of AD.

Verbal disfluency and anomia are often early features and sometimes the presenting feature of AD (40). The first manifestations of language dysfunction usually include word-finding difficulties, circumlocution, reduced vocabulary in spontaneous speech, and anomia on confrontational naming tests, which progress to include agrammatism, paraphasic errors, impoverished speech content, and impaired comprehension. Patients can usually repeat phrases verbatim until the disease is quite advanced (41).

Loss of visuospatial skills is an early feature of AD that is sometimes very prominent at presentation (42-44). Visuospatial impairments manifest as misplacement of items and difficulty navigating in first unfamiliar, and as deficits progress, familiar terrain. Visual agnosia (inability to recognize objects) and prosopagnosia (inability to recognize faces) are later features. Some clinicians have noted hemispatial visual neglect in their patients with AD (45, 46).

In early stages of AD, impairment of executive function is usually subtle (47); family members and coworkers may find them less motivated, less engaged, and apathetic. As the disease progresses, a more manifest alteration of personality, poor judgment and planning occurs, and inability to complete tasks typically emerges. Reduced insight into deficits (anosognosia) is a characteristic feature of AD and has been linked to frontal lobe pathology (48, 49). Those with relatively preserved insight are more likely to be depressed; those with more impaired insight are likely to be agitated, disinhibited, and exhibit psychotic features such as hallucinations, delusions or misidentification syndromes (50, 51). Neuropsychiatric symptoms are common in AD, particularly in the middle and late course of disease.

Other signs and symptoms worth mentioning are dyspraxia and apraxia, which usually occur later in the disease after deficits in memory and language have become apparent, then changes in olfactory function, sleep disturbances (fragmented sleep), seizures, and pyramidal and extrapyramidal motor signs, which are typically late-stage findings.

The criteria for the diagnosis of probable AD dementia have been established by the National Institute on Aging and the Alzheimer's Association (NIA-AA) and most recently updated in 2011 (5, 7). Probable AD dementia is a syndrome of dementia defined by the following characteristics:

- interference with the ability to function at work or at usual activities;
- a decline from the previous level of functioning and performing, not explained by delirium or major psychiatric disorder;
- cognitive impairment established by history-taking from the patient and a knowledgeable informant; and objective bedside mental status examination or neuropsychological testing;
- cognitive impairment involving a minimum of two of the following domains: impaired ability to acquire and remember new information; impaired reasoning and handling of complex tasks; poor judgment; impaired visuospatial abilities; impaired language functions; changes in personality, behavior or comportment;
- insidious onset;
- clear-cut history of worsening;
- initial and most prominent cognitive deficits are one of the following : 1) amnestic presentation (i.e. impairment in learning and recall of recently learned information); 2) nonamnestic presentations include either a language presentation, with prominent word-finding deficits; a visuospatial presentation, with visual cognitive deficits; or a dysexecutive presentation, with prominent impairment of reasoning, judgment and/or problem solving); and
- no evidence of substantial concomitant cerebrovascular disease, core features of dementia with Lewy bodies, prominent features of behavioral variant frontotemporal dementia or prominent features of semantic or nonfluent/agrammatic variants of primary progressive aphasia, or evidence of another concurrent, active neurologic or nonneurologic disease or use of medication that could have a substantial effect on cognition (5,7).

The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for AD are also commonly used and were revised in 2013 (52). The DSM-5 definition of probable AD (now called major neurocognitive disorder due to AD) and include the following:

- evidence of significant cognitive decline from a previous level of performance in one or more

cognitive domains (learning and memory; language; executive function; complex attention; perceptual-motor; social cognition);

- cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications;
- cognitive deficits do not occur exclusively in the context of a delirium;
- cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia);
- there is insidious onset and gradual progression of impairment in at least two cognitive domains; and
- either of the following:
  1) evidence for a causative AD genetic mutation from family history or genetic testing; and
  2) all three of the following are present: (a) clear evidence for decline in memory and learning and at least one other cognitive domain; (b) steadily progressive, gradual decline in cognition, without extended plateaus; (c) no evidence of mixed etiology (i.e. absence of other neurodegenerative disorders or cerebrovascular disease, or another neurologic, mental or systemic disease or condition contributing to cognitive decline) (52).

CONCLUSION

Alzheimer's dementia is the most common form of neurodegenerative dementia. As age remains the strongest risk factor for AD, the incidence of AD increases exponentially after the age of 60. The pathophysiological process begins more than a decade prior to the clinically developed symptoms and this period may be the optimal time to intervene. Old diagnostic criteria from 1984 were based entirely on clinical symptoms, while the new criteria from 2011 onwards consider AD as a continuum that encompasses three different disease stages: preclinical phase, symptomatic pre-dementia phase (MCI) and dementia phase (AD). Newer criteria place emphasis on using biomarkers to provide an earlier and more specific diagnosis in order to ensure effective treatment.

The role of laboratory (CSF biomarkers) and imaging (CT, MRI, PET, SPECT, fMRI, amyloid PET tracers) is to exclude other diagnoses, to support the diagnosis of AD or some of them are used in research settings in an effort to better define prodromal and preclinical forms of AD and identify candidates for early, intervention clinical trials. Effective strategies for early diagnosis, prevention and treatment are urgently needed.

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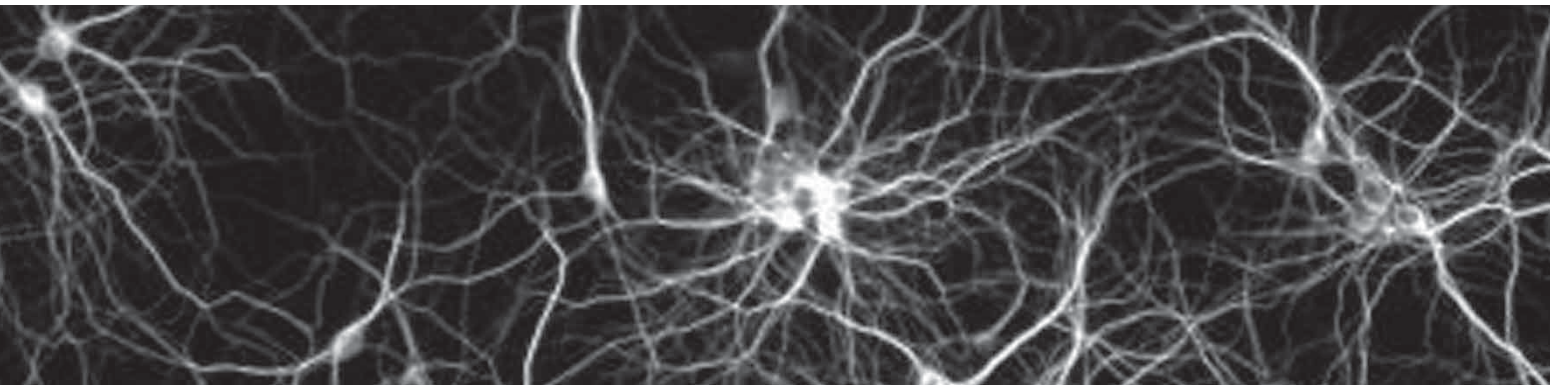
Novi dijagnostički kriteriji za Alzheimerovu bolest

SAŽETAK - Cilj ovoga pregleda bio je istražiti dosad objavljene kriterije za dijagnosticiranje Alzheimerove demencije koji se primjenjuju u kliničkoj praksi. Danas smo u mogućnosti istraživati okolišne čimbenike i genetsku predispoziciju za razvoj Alzheimerove demencije, otkriti biomarkere u cerebrospinalnom likvoru i neuroadiološke karakteristike same bolesti te na kraju uočiti brojne kliničke manifestacije pred-dementne i dementne faze. U upotrebi su dijagnostički kriteriji NIA-AA (*National Institute on Aging and the Alzheimer's Association*) iz 2011. godine te kriteriji DSM 5 (*The Diagnostic and Statistical Manual of Mental Disorders*) iz 2013. godine koji imaju približno podjednaku učinkovitost u kliničkoj praksi. Potrebna su daljnja istraživanja kako bi se definirali još specifičniji i osjetljiviji dijagnostički kriteriji te što učinkovitiji način liječenja.

Ključne riječi: Alzheimerova bolest, dijagnostički kriteriji, biomarkeri



Small fiber neuropathy – how to start, where to go?

Valentina Delimar, Olga Miloš, Ervina Bilić

ABSTRACT - Small fiber neuropathy (SFN) is a type of sensory neuropathy which selectively affects small diameter somatic and autonomic nerve fibers. Diagnosis is challenging, given that clinical picture can be difficult to interpret. Patients typically present with painful paresthesias and/or signs of autonomic dysfunction. In SFN, neuropathic pain was shown to be a frequent and early symptom, so it is considered as a reliable marker of this neuropathy. The diagnosis of SFN relies on clinical features combined with abnormal quantification of intraepidermal nerve fiber density (IENFD) and/or deficit in temperature threshold on quantitative sensory testing (QST). SFN is associated with various systemic diseases, among which diabetes was found to be the most common one. This knowledge urges a detailed diagnostic work-up of every patient presenting with SFN because new understanding of the SFN etiology could help narrow the proportion of idiopathic SFN patients, which is still large. Most recent discoveries of several novel mutations to sodium channels in patients with idiopathic SFN could help in this area, as well as in the development of specific treatment options. For now, the treatment of SFN is very complex. Causative therapy is advised whenever possible and symptomatic treatment should follow newest guidelines on the management of neuropathic pain in general.

Key words: small fiber neuropathy, neuropathic pain, skin biopsy, quantitative sensory testing

INTRODUCTION

Small fiber neuropathy (SFN) is a type of sensory neuropathy characterized by painful paresthesias or signs of autonomic dysfunction. SFN is associated with various metabolic, infectious, inflammatory and genetic diseases, but in the majority of cases the cause is idiopathic. The incidence and prevalence of SFN is unknown (1). SFN affects both small somatic and autonomic fibers. Affected fibers are small myelinated Aδ fibers and small unmyelinated C fibers, the sensory function of which includes thermal perception and nociception (2,3). Aδ myelinated fibers are the main afferents for cold

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perception, and they are also involved in cutaneous nociception. Unmyelinated C fibers play a role in warm perception and only a minor role in cold thermoperception (2). Small fibers are also involved in a number of autonomic and enteric functions (3).

Over the last decade, SFN and its diagnosis has become of great interest, especially since the introduction of quantification of intraepidermal nerve fiber density (IENFD) in skin biopsies (1,4). Various studies have proposed different definitions for SFN (1,2,5). According to recent findings, the diagnosis of SFN relies on clinical features combined with abnormal quantification of IENFD and/or deficit in temperature threshold testing (1). The diagnosis of SFN should be graded as possible, probable or definite (6). Possible SFN requires presence of length-dependent symptoms and/or clinical signs of small fiber damage. Probable SFN requires presence of length-dependent symptoms, clinical signs of small fiber damage and normal sural nerve conduction study (NCS). Definite SFN includes length-dependent symptoms, clinical signs of small fiber damage, normal sural NCS and altered IENFD at the ankle and/or abnormal quantitative sensory testing (QST) thermal thresholds at the foot (6). These criteria were originally proposed for diabetic SFN, but they should be applied in each patient irrespective of the underlying cause (6).

PATHOGENESIS AND ETIOLOGY

Specific etiology of SFN is mostly unknown. In some cases, SFN is part of an underlying systemic disease, including different metabolic, immune-mediated, genetic or infectious diseases. It can also be a consequence of the intake of drugs or toxins (6,7).

Diabetes and impaired glucose tolerance (IGT) stand out as the most common from the metabolic group of diseases (2,6,8). The majority of older patients with SFN have prediabetes or diabetes, while IGT was found to be frequent in cases of idiopathic SFN, with a prevalence of 34%-35.6% (2,9,8). In patients with diabetes, various tests assessing sudomotor dysfunction showed good predictive value for detecting SFN. This is very important, considering that these tests are noninvasive and that sudomotor dysfunction is one of the early signs of SFN in diabetic patients (8,10). Some patients with diabetes may experience an acute painful SFN called insulin neuritis, which is associated with rapid glycemic control (3,6). In a long-term follow-up Oslo study, SFN was found as a major manifestation in type 1 diabetes. This study showed that small fiber damage was even more prevalent than large fiber neuropathy, which was explained by greater sensitivity of small nerve fibers to metabolic changes, such as changes in blood glucose level (11). Considering that sensory small fibers are predominantly involved in diabetic neuropathy, it is advisable to understand its pathophysiology because a connection to understanding SFN in other systemic diseases could also be found (9).

The pathophysiology of diabetic neuropathy is multifactorial, with hyperglycemia being the central factor. There are three main metabolic effects of hyperglycemia on nerve function, including activation of the polyol pathway, formation of advanced glycosylation end products (AGEs) and changes in the metabolism of essential amino acids. Hyperglycemia increases the activity of polyol pathway, which leads to the accumulation of sorbitol and fructose in the peripheral nerve axons. This causes osmotic influx of water and cell edema, which in turn damages Ranvier's nodes and nerve conduction velocity. Accumulation of sorbitol also causes diminution of myo-inositol and taurine concentration, which interferes with the activity of Na+-K+-ATPase and causes more pronounced cell edema. Finally, excessive activation of the polyol pathway results in a decrease of reduced nicotinamide adenine dinucleotide phosphatase (NADPH) and oxidized nicotinamide adenine dinucleotide (NAD+), which leads to decreased synthesis of reduced glutathione and nitric oxide causing in the end massive oxidative stress. Disorder of amino acid metabolism causes changes in nerve membrane structure, microvascular abnormalities and changes in nerve excitability, while lipid peroxidation reduces nerve conduction velocity. Nonenzymatic glycosylation produces AGEs, which cause microvascular damage, glycation of tubulin, other neurofilaments and myelin. Macrophages cause glycated myelin phagocytosis and cause demyelination. This damages the structure of nerve fibers and Schwann cells. In addition, AGEs contribute to oxidative stress by creating free radicals (12). Oxidative stress stands out as the main factor in the pathogenesis of diabetic neuropathy and a growing body of evidence implicates its importance in different diseases causing SFN (7,13-19). Effects of hyperglycemia on nerve function are shown in Fig. 1. There is a large overlap between diabetes and metabolic syndrome. Patients with diabetes and metabolic syndrome appear to have twice the risk of developing SFN compared to those with diabe-

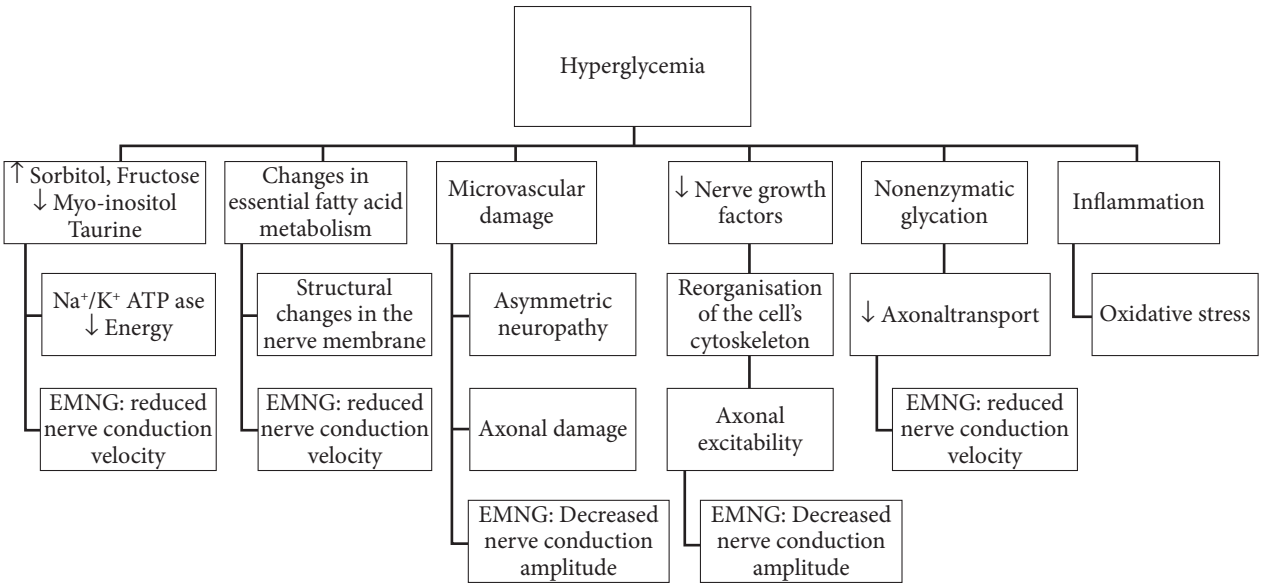

Fig. 1. *Effects of hyperglycemia on nerve function.*

tes alone. All factors of metabolic syndrome (hyperlipidemia, hypertension, obesity, abnormal glucose metabolism and insulin resistance) convey an increased risk of developing SFN. Studies suggest that hyperlipidemia is the single largest contributor to the development of neuropathy, especially elevated serum triglycerides (>800 mg/dL) (2,3). Other less common metabolic diseases associated with SFN include hypothyroidism and vitamin B12 deficiency (5,6,20).

Different immune-mediated diseases are connected with SFN, but the underlying mechanism is not entirely explained. Supporting data mainly relate to good therapeutic response to immunoglobulin or immune-suppressant treatments (6,7,21). Several pharmacological and physiological studies give support to an immune-mediated role, considering that proinflammatory cytokines are involved in the generation and maintenance of neuropathic pain (7) (22-24). Small nerve fibers were found to be more vulnerable to ischemia than large diameter nerve fibers, so damage to small fibers due to ischemia was suggested in patients with vasculitis (7,25,26). Decreased antioxidant defense capacity was found in patients with sarcoidosis (7,19). Other immune-mediated diseases associated with SFN include Sjögren's syndrome, celiac disease, systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel diseases, paraneoplastic syndrome, monoclonal gammopathy and complex regional pain syndrome type 1 (2,6). Among genetic diseases, SFN was found in hereditary sensory autonomic neuropathy (HSAN) type IV, Fabry's disease, familial amyloidosis, hemochromatosis and familial burning feet syndrome (6). Most recent studies found gain-of-function mutations in sodium channels Na(V)1.7 and Na(V)1.8 in some SFN patients (27,28). *SCN9A*-gene variants (single amino acid substitutions) were found in ~30% of a cohort of idiopathic SFN patients, producing gain-of-function changes in sodium channel Na(V)1.7, which is preferentially expressed in small diameter peripheral axons (27). Na(V)1.8 mutations were found more recently in patients with idiopathic SFN (28). Both mutations cause hyperexcitability of small dorsal root ganglion (DRG) neurons and development of specific treatment in these patients seems a logical target for future studies (27,28).

Different infectious diseases and drugs are involved in the development of SFN, such as HIV, hepatitis C, influenza and usage of antiretroviral drugs, metronidazole, bortezomib, statins, nitrofurantoin, flecainide and linezolid (6). Chronic alcohol abuse in early stages causes predominantly SFN (2,6).

Despite the association of SFN with various acquired and genetic conditions, in a substantial proportion of patients (25% to 90%), the cause of SFN remains unknown (2,5-7). Progression of SFN is usually slow and spontaneous remission is rare (6,29). Over time, in some patients pure SFN can evolve to large fiber sensory neuropathy (2,6).

CLINICAL FEATURES

Symptoms of SFN can vary widely in severity and mostly have gradual onset (3). In most patients,

Table 1. *Differences in clinical picture and electrodiagnostic findings in small vs. large fiber neuropathy*

Type of neuropathy	Symptoms	Clinical signs	Electrodiagnostic findings
Large fiber neuropathy	– painful cramps and fasciculations – muscle atrophy – numbness without pain – tingling – weakness	– diminished deep tendon reflexes – reduced vibratory and position sense – muscle weakness	EMNG-abnormal: – slowed motor and sensory conduction velocities – reduced motor and sensory action potentials and denervation
Small fiber neuropathy	– *Positive*: burning feet, tingling, prickling, shooting pain or aching, allodynia, cramps – *Negative*: numbness, 'tightness', 'coldness' – *Autonomic*: increased/ decreased sweating, facial flushing, skin discoloration, dry eyes and mouth, presyncope/syncope, nausea, vomiting, diarrhea, constipation, difficulty with urinary frequency, erectile dysfunction, changes in skin temperature	– reduction in thermal and pain sensitivity – normal strength, proprioception and tendon reflexes – mostly normal vibratory sensation and light touch	– EMNG-normal – QST-abnormal: decreased temperature sensitivity

SFN starts distally in a length-dependent fashion, resulting in the loss of function in stocking distribution in lower extremities (3,6). A glove-like sensory loss in upper extremities appears when the condition is more advanced (3). In some cases, diffuse and asymmetric symptoms were described (6). Patients typically present with positive sensory symptoms and burning feet is the most common complaint reported. Other sensory symptoms include tingling, prickling, shooting pain or aching, while allodynia and cramps occur less often. Cramps usually affect calf muscles and may mislead clinicians to think of other diagnosis, such as metabolic disorders or drug side effects (7). However, it is important to think of SFN in these cases because a recent study revealed that 60% of patients with muscle cramps, who lacked neuropathic complaints, actually had SFN (29). Damage to small fibers frequently causes neuropathic pain, which occurs as an early symptom in SFN (5,9). Quality of pain may differ from spontaneous pain to thermally evoked pain and/or allodynia. It is commonly worse at rest and during the night (6). Negative symptoms of SFN include numbness, „tightness" and „coldness" (2,3,6). Regarding autonomic symptoms, patients may have increased or decreased sweating, facial flushing, skin discoloration, dry eyes and mouth, postural hypotension, presyncope or syncope, nausea, vomiting, diarrhea, constipation, difficulty with urinary frequency, nocturia, erectile dysfunction (occurs in up to 40% of males) and changes in skin temperature (2,3). Generally, patients experience sensory symptoms far more often than autonomic symptoms. If autonomic dysfunction is present, vascular deregulation in lower limbs is more frequent than cardiovascular autonomic impairment (2,5,6). Patients can sometimes present with late-onset restless legs syndrome (RLS). It is important to evaluate this type of patients for SFN, especially if they do not have positive family history of RLS (2,6,30). SFN has also been suggested in patients with focal burning pain and burning mouth syndrome (6).

Neurological examination of patients with SFN reveals normal to marginally pathological findings (31). There is a reduction in thermal and pain sensitivity in association with normal strength, proprioception and tendon reflexes. Light touch and vibratory sensation are mostly normal. Associated skin changes may include cracked, dry or shiny skin (2,3). Diagnosis of SFN is challenging, as the clinical picture can be difficult to interpret (32). Considering differential diagnosis, other conditions that may mimic SFN include venous insufficiency, spinal stenosis, myelopathy and psychosomatic disturbances (3). Distinguishing small from large fiber neuropathy is also important; the most common symptoms, clinical and electrodiagnostic findings are shown in Table 1.

DIAGNOSING SMALL FIBER NEUROPATHY

The new attitude towards SFN is that it should be considered as a complication of an underlying sys-

temic disease. Therefore, for all patients with SFN a detailed diagnostic work-up should be done (6). Frequently associated diseases like prediabetes and diabetes indicate the need of oral glucose tolerance test, fasting glucose and glycosylated hemoglobin tests (3,6). Next, testing for different autoimmune diseases like Sjögren's syndrome, sarcoidosis, SLE and celiac disease should be considered (6,7). Suspicion of amyloidosis rises in patients with dysautonomia and cardiac or liver involvement (6). In view of the most recent discovery of several novel mutations to sodium channels, screening of SCN9A gene should be considered, especially in patients with positive family history of SFN (6,33). Finally, neuropathic pain was shown to be a reliable marker of SFN (1). Considering that pain is a subjective phenomenon which patients are not always capable to describe properly, the use of different screening tools in clinical practice for identifying neuropathic pain is useful and important. One of the widely used screening tools for neuropathic pain is the PainDETECT questionnaire. This is a self-administered questionnaire that consists of nine items; 7 questions relate to the intensity of sensory symptoms and 2 questions relate to pain pattern and to radiation of pain to other parts of the body. PainDETECT was validated in a multicenter study in Germany, its sensitivity and specificity being rated as 85% and 80%, respectively (34). According to the final score on the questionnaire, pain is classified as nociceptive, unclear or neuropathic. Another efficient screening tool is the Total Neuropathy Score (TNS), which estimates subjective and objective aspects of peripheral nerve fiber function, as well as characteristics and duration of patient symptoms. This makes it one of the most capacious tools for clinical assessment of neuropathies (35). TNS analyzes sensory, motor and autonomic symptoms, pin and vibration sensibility, strength, tendon reflexes, QST vibration and thermal threshold, and NCS of sural and peroneal nerve (36).

There is only one validated tool designed specifically for assessing symptoms of SFN, the 13-item Small Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN-SIQ) (1,6). This questionnaire assesses the presence of several SFN specific sensory and autonomic symptoms and each item is scored on a 4-point Likert scale (1). SFN-SIQ was used for screening of patients with sarcoidosis and genetic sodium-channel associated SFN (6).

Patient medical history and clinical examination findings pose suspicion of SFN, but for confirmation of the diagnosis further neurophysiologic tests are needed. NCS, QST and skin biopsy are sorted out today as the most relevant diagnostic tests (1,6,37).

ELECTROMYONEUROGRAPHY

Clinical electromyoneurography is a diagnostic method that helps objectify damage to the peripheral nervous system. It consists of electromyography (EMG) and NCS. Considering that EMG and NCS are used to assess the integrity of larger myelinated sensory and motor fibers, they are generally normal in patients with pure SFN (3,6,7). Older patients are an exception because they may sometimes lack sural response in NCS, but they can still be diagnosed with SFN (2).

QUANTITATIVE SENSORY TESTING

Quantitative sensory testing is an important tool in assessing the function of small as well as large sensory fibers (2,7). Small caliber fibers are assessed by measuring temperature thresholds and heat pain thresholds, whereas large caliber fibers are assessed by measuring vibration thresholds (7).

Two general schemes are used in QST: the method of levels and the method of limits. Delivered thermal stimuli consist of a ramp of ascending (warm) and descending (cool) thermal energy delivered through a thermode (7). In the method of levels, the patient receives standardized stimuli and has to signal whether a specific level is detected. This method is also referred to as a „forced choice" algorithm. This method takes longer to complete, which makes it susceptible to errors from decreased attention by the patient. Consequently, reliability of the results can come in question. In the method of limits, the patient receives stimuli the intensity of which increases or decreases over time at a predefined speed. The patient has to indicate as soon as he starts or stops detecting the stimuli (12,38). The same stimuli are repeated 3-5 times and the threshold is calculated statistically (12). Physical properties of the stimuli must be standardized, including the area of application, intensity, duration and rate of stimulus application (39). Quality reference values must be available and patients must be tested in the appropriate environment. Many studies confirm the efficacy of QST in diagnosing SFN, and its sensitivity ranges from 60% to 85% (2). Limitations of QST are the following: testing is subjective, patient must be concen-

trated and cooperative, which may lead to difficulties during testing in conditions of cognitive impairment, and abnormalities in either the central or peripheral nervous system can result in the same deficit on the test. There are different equipment types among laboratories and due to a relatively broad range of normality of small fiber function, some patients with SFN may be undetected (2,3). QST is useful in detecting SFN, but it needs to be used in a clinical context and along with other diagnostic tests (6).

SKIN BIOPSY

Skin biopsy is considered to be the most accurate method to diagnose SFN (1,4,5,37). It has higher diagnostic accuracy compared with clinical features and QST results (1). The sensitivity (74%-90%) and specificity (64%-90%) are high across many studies (37). Skin biopsy confirms reduction of the IENFD in SFN and biopsy should be taken 10 cm above the lateral malleolus, within the sural nerve territory (6). Normative reference values for IENFD at the distal leg based on the 5th percentile cut-off adjusted *per* age decade and sex are available for bright-field immunohistochemistry (6,40).

OTHER DIAGNOSTIC TESTS

The following diagnostic tests were found useful in some studies, but most of them are still not implemented in broad clinical use. This includes various tests of sudomotor function, with the exception of quantitative sudomotor axon reflex test (QSART), cardiovascular reflex testing, current perception threshold testing (CPT), sural nerve biopsy, laser-evoked potentials, contact heat-evoked potential stimulators (CHEPs), microneurographic C-fiber recordings, laser Doppler flowmetry (LDF), meta-iodobenzylguanidine (^{123}-I-MIBG) scintigraphy, blister biopsy and corneal confocal microscopy (2,6,7). Results of corneal confocal microscopy showed high correlation with skin biopsy results in SFN patients (6). Considering that this is a noninvasive technique, further research is advisable to implement it in everyday clinical practice. A recent study has pointed out that assessment of autonomic function of small fibers is not included in the official diagnostic procedures for SFN (41). QSART provides a quantitative, validated assessment of postganglionic sudomotor function and studies have suggested that it is frequently abnormal in patients with SFN. Therefore, implementation of QSART in the diagnosis could enhance the diagnostic criteria for SFN (41).

THERAPY

Treatment of SFN is very complex because there is limited evidence for specific therapy (3). Causative therapy, depending on the underlying disease, should be given whenever possible. This usually includes antidiabetic drugs, steroids, immunosuppressants or intravenous immunoglobulin (IVIG) treatment (6). If there is no specific identifiable cause found, therapy is usually focused on treating neuropathic pain, for which updated guidelines are available (2,6,7,42,43). As first line treatment, tricyclic antidepressants (TCA), gabapentin, pregabalin and selective norepinephrine and serotonin reuptake inhibitors (SNRI) are recommended. Tramadol is recommended as second line therapy, with the exception of patients with predominant coexisting non-neuropathic pain and those with exacerbations of pain, where it can be given as a first line therapeutic option. Strong opioids are recommended as third line therapy because of their addiction potential and misuse (43).

It is important to note that most clinical studies examined drugs in the treatment of different neuropathic pain syndromes, and not specifically pain secondary to SFN (3,6). This represents a challenge in developing SFN treatment recommendations because most of the studies focused on SFN included a limited number of patients without long term follow up. For example, Ho *et al*. showed that both gabapentin and tramadol were found to be effective in the treatment of SFN in comparison with placebo (44). Hong *et al*. describe a case of type 2 diabetic peripheral small fiber neuropathic pain successfully treated with whole body vibration therapy, after a failed trial of conventional drugs and interventional pain management (45). Wakasugi *et al*. describe a patient with Sjögren's syndrome who developed SFN and was treated with IVIG therapy, which proved immediately and extremely effective (46). Hedstrom's study indicated that topical application of GFRα/RET receptor signaling modulators may be a unique therapy for SFN (47). Considering that SFN has an overall severe impact on the quality of life, future studies are warranted to determine the best possible treatment (1).

CONCLUSION

Small fiber neuropathy is a relatively common disorder, which is often underdiagnosed and undertreated. Suspicion of SFN is based on medical history and neurological examination. Standard electrophysiological tests such as EMG and NCS are

normal, so the diagnosis can only be confirmed with additional diagnostic work-up, such as QST and IENFD. Neuropathic pain was shown to be a frequent and early symptom of SFN. Due to commonly associated metabolic, immune-mediated and genetic diseases, it is important to do adequate diagnostic work-up when dealing with painful neuropathy. Early diagnosis is crucial because it can lead to prompt initiation of causative or symptomatic treatment. Future studies are needed to find best treatment possibilities and to determine the pathophysiology of SFN. The answer to the question from the title could be: "Start with detailed neurologic examination and go to the site where SFN has begun".

LITERATURE SEARCH STRATEGY

We conducted a review of the original papers and review articles indexed in Current Contents, PubMed, Medline and Google Scholar between 1982 and 2013. We used several terms individually or in combination including small fiber neuropathy, painful neuropathy, diagnostic criteria, neuropathic pain, screening tools, quantitative sensory testing, intraepidermal nerve fiber density, diabetic polyneuropathy, and idiopathic. Only articles on adult population were reviewed.

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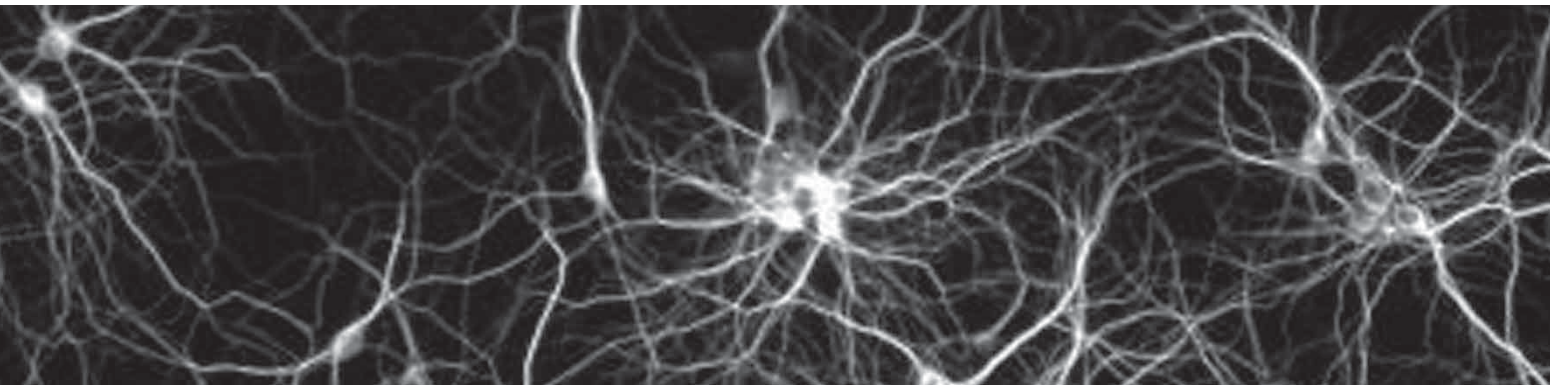
Neuropatija tankih vlakana - kako početi, kamo ići?

SAŽETAK - Neuropatija tankih vlakana (NTV) je vrsta senzorne neuropatije koja zahvaća tanka somatska i autonomna živčana vlakna. S obzirom na to da je klinička slika ponekad atipična, postavljanje dijagnoze NTV-a je zahtjevno. Kod pacijenata su najčešće prisutne bolne parestezije i/ili znakovi autonomne disfunkcije. Neuropatska bol je česta i manifestira se vrlo rano u tijeku bolesti te se danas smatra pouzdanim biljegom NTV-a. Dijagnoza se postavlja temeljem neurološkog pregleda i patološkog nalaza na kožnoj biopsiji i/ili mjerenju praga osjeta za temperaturu na kvantitativnom senzornom testiranju (KST). NTV je povezana s različitim sistemnim bolestima, s time da se dijabetes izdvaja kao najčešća. Ova saznanja upućuju na to da je svakog pacijenta s NTV-om potrebno detaljno dijagnostički obraditi u smislu podležeće bolesti, jer bi upravo novi podaci o etiologiji NTV-a mogli utjecati na smanjenje udjela pacijenata s idiopatskim NTV-om koji još uvijek zauzima značajan udio. Najnovija istraživanja otkrila su postojanje novih mutacija natrijevih kanala u pacijenata s idiopatskim oblikom, što bi u budućnosti moglo razjasniti etiologiju NTV-a te utjecati na razvoj ciljane terapije. Zasada je terapija NTV-a veoma složena. Ako je moguće, liječi se podležeća bolest koja je dovela do neuropatije, dok se u ostalim slučajevima savjetuje simptomatska terapija neuropatske boli u skladu s najnovijim dostupnim smjernicama.

Ključne riječi: neuropatija tankih vlakana, neuropatska bol, kožna biopsija, kvantitativno senzorno testiranje



Third ventricular chordoid meningioma or chordoma: a diagnostic dilemma based on a single case

Krešimir S. Đurić, Goran Mrak[1], Jakob Nemir, Antonia Jakovčević[2], Kamelija Žarković[3], Pavle Miklić[1]

ABSTRACT - We report a case and literature review of a rare third ventricular tumor in a child with histologic characteristics of chordoma and chordoid meningioma (CM). *Case*: A 13-year-old boy was diagnosed with a recurrent intraventricular tumor 22 months after complete surgical removal. Reoperation was indicated; treatment consisted of total microsurgical removal, histologic and immunohistochemical classification, and follow up. Literature review on Pub Med was performed using the Mesh key words: "Cerebral Ventricle Neoplasms" AND "Pediatrics". Histologic and immunohistochemical analysis after the first operation had shown chordoma, and second histologic and extended immunohistochemical analysis showed positivity for D2-40 marker, which is negative in chordoma but can be positive in CM. It was concluded to be a case of CM. Fourteen months after reoperation there were no signs of tumor recurrence. Literature review showed two cases of intraventricular CM, one situated in lateral ventricle and the other in third ventricle. *Conclusion*: This is the second reported case of CM situated in the third ventricle in a pediatric patient. In this case, follow up was performed regularly for 22 months after the first complete resection, when the tumor recurred. First histologic and immunohistochemical analysis showed chordoma, whereas second analysis showed CM. Fourteen months after reoperation there were no signs of tumor relapse. The boy returned to his everyday activities, with some hormone misbalance treated with hormone substitutes.

Key words: intraventricular meningioma, chordoid meningioma, pediatrics, chordoma, immunohistochemistry

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INTRODUCTION

Chordoid meningioma (CM) tumor was first described by Kapes *et al*. in 1988 (13). It is estimated that CM account for less than 0.5%-1% of all meningiomas (4, 5). In the latest World Health Organization (WHO) tumor classification system, CM is graded as atypical (GII grade) meningioma because of a high rate of recurrence after surgical resection (14, 18).

Morphologically, CM is composed of epithelioid or spindle cells that form cords or nests in a basophilic mucoid matrix resembling physaliferous cells of the chordoma. Diagnosis is made morphologically and immunohistochemically but in some cases the exact diagnosis can be difficult because the minority of CM are focally positive for S-100 protein (S-100) and pan-cytokeratin (pan-CK), markers typically associated with chordomas (6).

Chordomas account for less than 0.2% of primary intracranial tumors (23), typically arising along the midline of neuroaxis at the sacrococcigeal (50%-60%), skull base (25%-35%) and vertebral (15%) region (8). Peak incidences are reported in the sixth decade of life and are uncommon in patients below thirty years of age (11). It is believed that they originate from vestigial cell remnant of the primitive notochord (21) or from benign notochordial cell tumor (2). They are mainly extra-dural intraosseous lesions that are locally aggressive, posing a challenge to treat. Intradural intracranial location is rarely reported. Intradural, extraosseous localized chordomas tend to have good prognosis when compared to intraosseous classical chondromas (10). Intraventricular localization without dural involvement is described in only one case (1).

There are 19 cases of CM in pediatric population (16,17,22) reported in the literature. To the best of our knowledge, there are two described cases of intraventricular CM in pediatric population, situated in the left lateral ventricle and third ventricle one each (17,22).

In this article, we report a third ventricular CM in a child, diagnosed, treated and followed-up at our department.

CASE REPORT

An 11-year-old, previously healthy Caucasian boy underwent diagnostic examination for evaluation of occasional tremor of his left hand experienced for several months. Neurological examination showed no abnormalities. Brain computed tomography (CT) revealed a large mass located in the

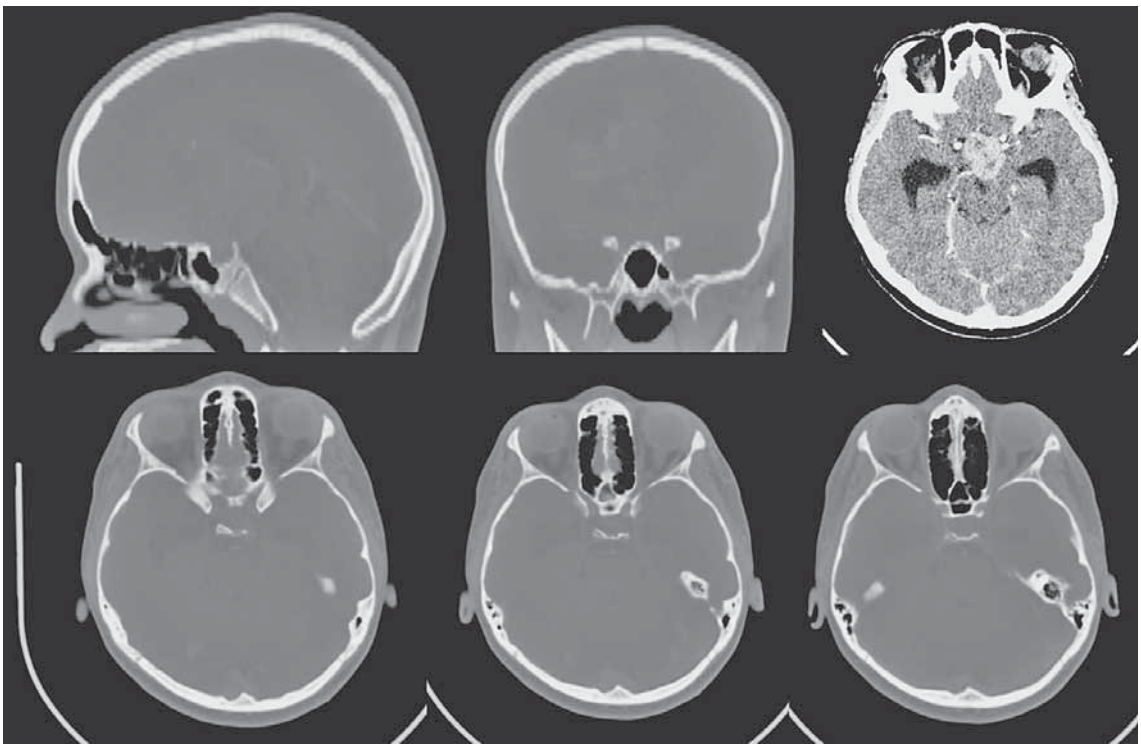

Fig. 1. *CT scan showing a large mass located in the third ventricle, measuring 6.3x5.0 cm, with supra- and retrosellar extension and no bone erosion.*

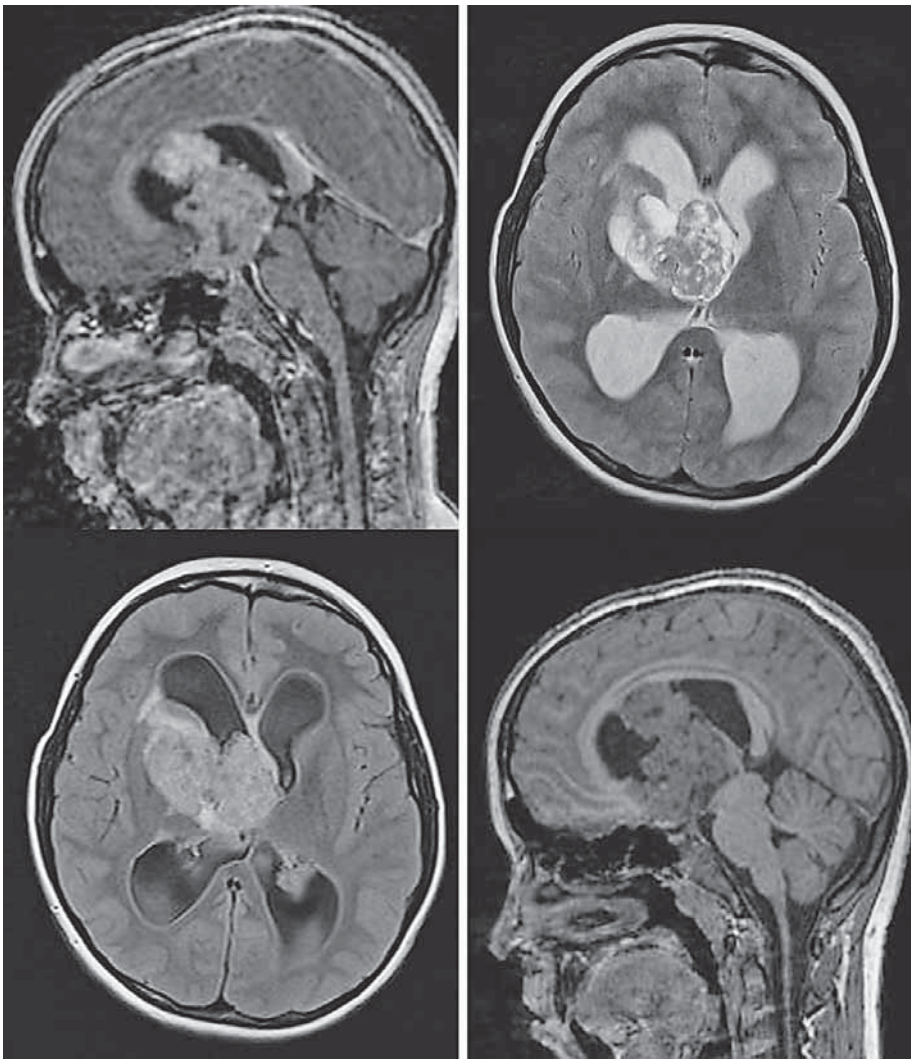

Fig. 2. *MRI scan showing a large, well-delineated mass measuring 6.3x4.2x5.0 cm, situated suprasellarly, involving the hypothalamic region with cranial extension at the third and right lateral ventricles. T2 sequence showed hypointense areas of calcifications. Post contrast sequence showed focal areas of enhancement. Internal cerebral veins are displaced by the tumor. Basal ganglia at the right side show perifocal edema. Dilated lateral ventricles and morphological loss of gyral and sulcal formations at the cortex are evident.*

third and right lateral ventricles, measuring 6.3x5.0 cm with supra- and retrosellar extension and no bone erosion (Fig. 1). Funduscopy showed papilledema. The patient was admitted to the hospital and magnetic resonance imaging (MRI) showed a large, well-delineated mass measuring 6.3x4.2x5.0 cm, situated suprasellarly and involving the hypothalamic region with cranial extension at the third and right lateral ventricles. MRI T2 sequence showed hypointense areas of calcification. Post contrast sequence showed focal areas of enhancement. Internal cerebral veins were displaced by the tumor. Basal ganglia at the right side showed perifocal edema. Dilated lateral ventricles and morphological loss of gyral and sulcal formations at the cortex were evident (Fig. 2).

SURGICAL PROCEDURE AND CLINICAL COURSE

The surgery was indicated soon after diagnosing the third ventricular tumor. The tumor was approached transcallosally interforniceally in general anesthesia and supine position, and completely removed using microsurgical technique with CT image guidance. No dural erosion was found intraoperatively. The tumor was completely removed (Fig.

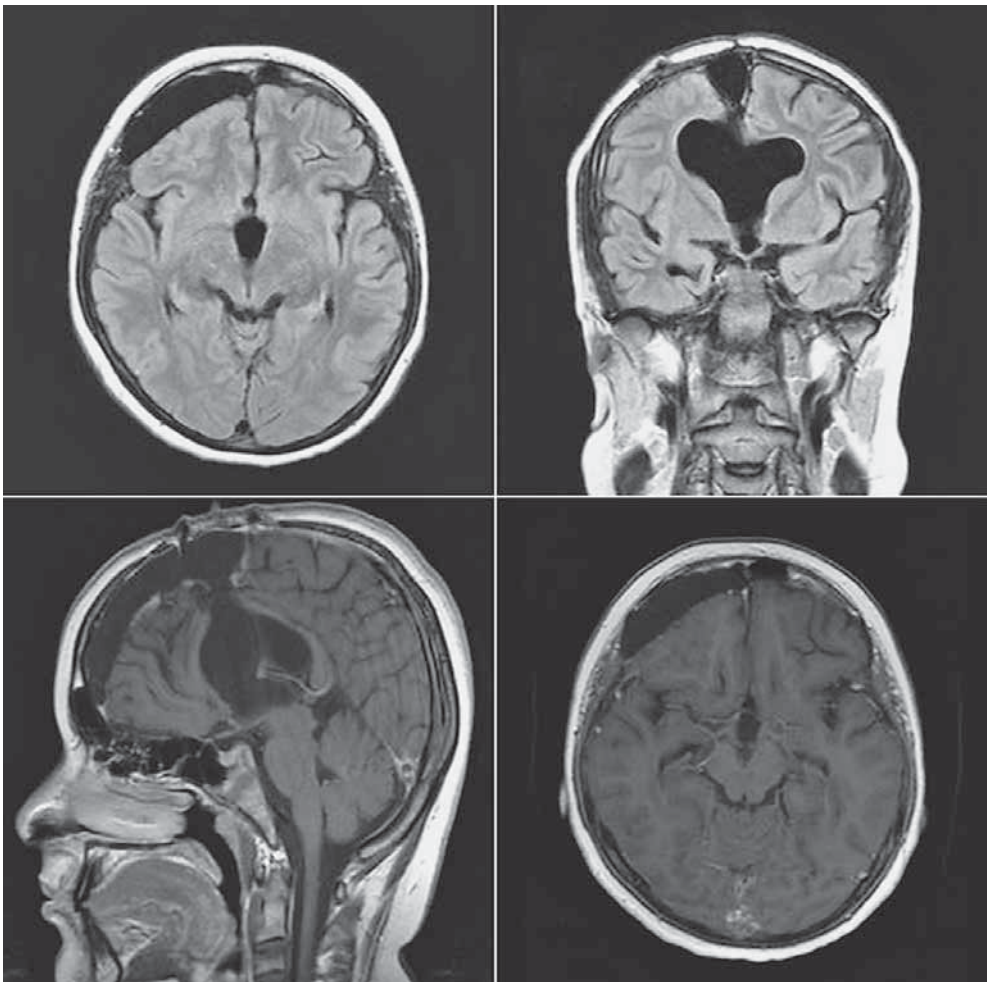

Fig. 3. *MRI acquired a month after the surgery showing complete tumor removal without new neurosurgical complications.*

3) and the tissue was sent for definite histologic examination. The postoperative course was complicated with short lasting polyuria and high potassium blood level on day 2, one episode of convulsions on day 5 and meningitis diagnosed on day 8 postoperatively. After the treatment of meningitis, the boy was transferred to the rehabilitation center with hydrocortisone as hormone replacement therapy. Periodic pediatric endocrinological follow up was performed regularly and hydrocortisone in low doses was continued as hormone replacement therapy. Follow up funduscopy showed no papilledema. The child resumed his everyday activities. Neurosurgical follow ups were performed regularly and 22 months after the surgery, tumor recurrence was evident on MRI (Fig. 4).

The second surgery was performed and the tumor was approached as previously described and completely removed. The postoperative course was uneventful and after brief rehabilitation, the child returned to his everyday activities. He attends regular school but has slightly lower grades. Fourteen months after the second surgery, follow up MRI showed no tumor (Fig. 5). Periodic pediatric endocrinological follow ups are performed regularly. Hydrocortisone in low doses is continued as hormone replacement therapy.

HISTOLOGIC FINDINGS

First histopathology analysis

The tumor was composed of moderately polymorph cells in diffuse or lobular pattern, separated by fibrous septa of varying thickness. The cells were embedded in abundant basophilic alcian blue positive mucinous matrix. The cells had oval eccentric nuclei with a dense chromatin pattern. Some cytoplasm contained vacuoles of various size and other cells had a more solid eosinophilic (periodic acid Schiff, PAS) positive cytoplasm. The tumor had areas of pleomorphic cells. Mitoses were absent. The

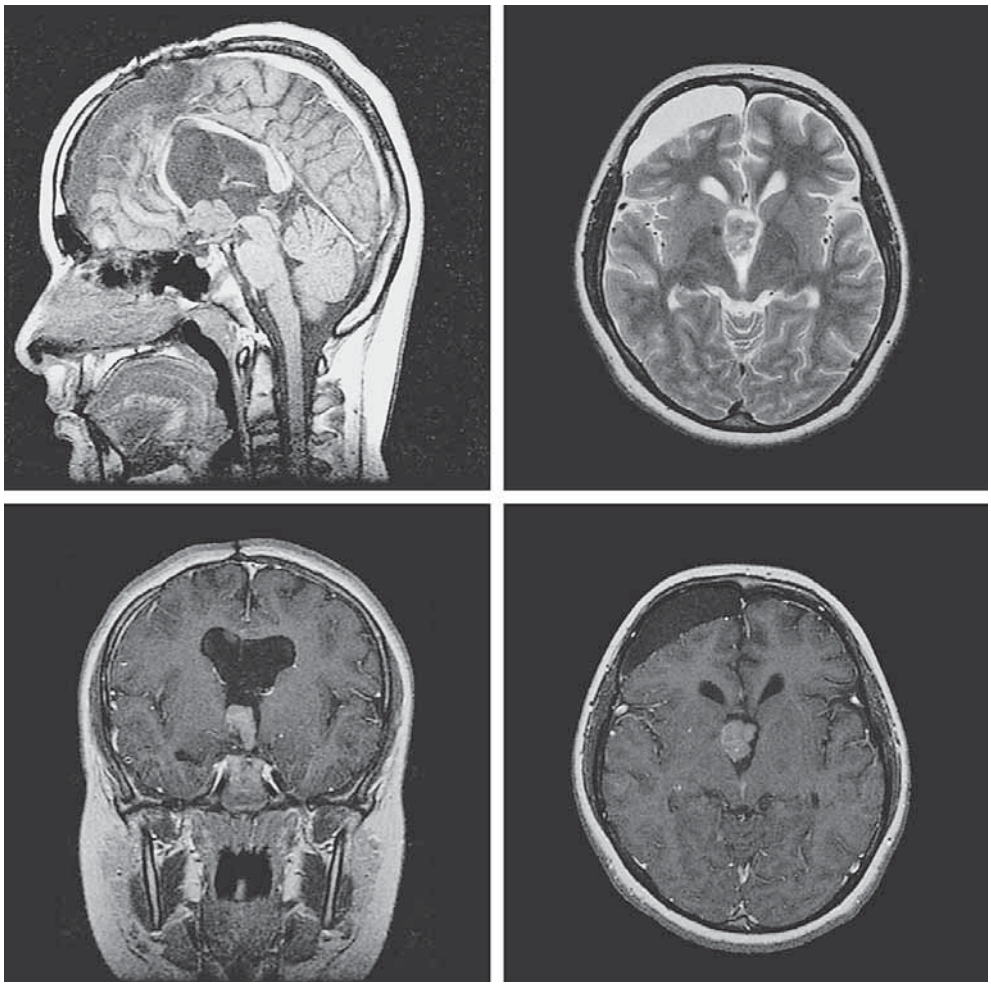

Fig. 4. *MRI acquired 22 months after the surgery showing tumor recurrence situated in the third ventricle.*

calcification and hemorrhage were uncommon. All tumor cells were strongly positive for epithelial membrane antigen (EMA) and vimentin (VIM). S-100 protein marker (S-100) was positive in most of the cells with a medium intensity and pan-cytokeratin (AE1/AE3) was partially positive in tumor cells. Immunostaining for glial fibrillary acidic protein (GFAP), actin (AC), chromogranin (Chg) and melanoma marker (HMB45) were negative. Ki-67 was 3%. The tumor was well demarcated from the surrounding brain tissue. The diagnosis was chordoma (Fig. 6).

Second histopathology analysis

The second histopathology analysis showed the same histologic characteristic except for the presence of one mitosis. Extended immunohistochemical staining showed positivity for D2-40 marker and sporadic and very weak S-100 positivity. In addition, D2-40 was performed on paraffin blocks from the first operation and it was positive in tumor cells. Ki-67 was 3%. Based on the morphology and immunohistochemical results, the diagnosis of CM was established (Fig. 6).

DISCUSSION

It is believed that chordomas originate from notochordial vestigial cell remnant that is demonstrated along the neuroaxial skeleton from sella turcica to the sacrum (6). They are situated intraosseously, which is the main radiological feature of these tumors. Intradural localization is exceptional (20).

The third ventricular chordoma has previously been described in only one case, as reported by Antigüedad *et al*. 1989 (1). The evidence available is suggesting that intradural chordomas have better prognosis if complete resection is achieved, in contrast to intraosseous classical chordomas (10,12,20). Further studies with longer follow ups are needed to support this clinical observation.

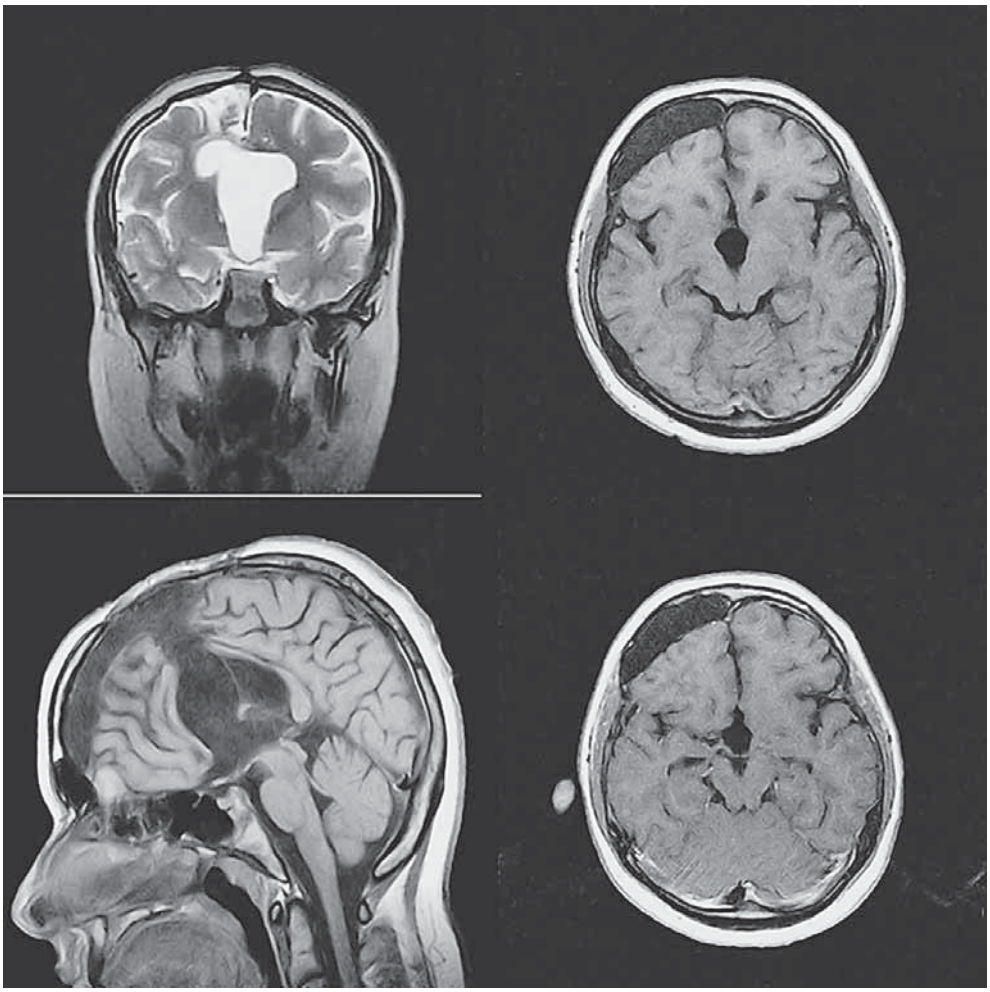

Fig. 5. *MRI acquired 14 months after the operation showing complete tumor removal and no signs of tumor recurrence.*

Intraventricular meningiomas arise from arachnoid cap cells trapped in the choroid plexus or velum interpositum during embryologic formation of the choroid fissure and plexus (7,15). It is estimated that 12% of reported meningiomas in pediatric population are situated within the ventricle. There are many series reporting a higher incidence of atypical and malignant variants of meningioma in children as compared with adults (19).

Chordoid meningiomas account for 0.5% to 1.0% of intracranial meningiomas (4,5). The tumor entity was first described by Kepes *et al*. in 1988; in 1993, it was classified separately as grade (G) I meningioma in the WHO classification (13,14). In the last WHO tumor classification revision from 2007, CM has been graded as atypical G II meningioma after the aggressive tumor behavior was described (18).

Histologically, CM is characterized by epithelioid cord-like tumor cells embedded in a myxoid stroma. Characteristic tumor cells with vacuolated cytoplasm strongly resemble physaliferous cells of chordoma. Morphologically, the diagnosis of CM is made when correct identification of the vacuolated trabeculae of neoplastic cells in a myxoid stroma is accompanied by co-existing areas typical of meningioma. The differential diagnosis includes chordoma, chordoid glioma, chondrosarcoma, myxopapillary ependymoma, metastatic mucinous and renal cell carcinoma. The accurate diagnosis is made on immunohistochemical profile but can be difficult because of overlapping in the morphological and immunohistochemical profiles (3) (Table 1).

In our case, the tumor showed morphologically chordoid and meningiomatous structure. Immunohistochemically, there was strong positivity for VIM, EMA and pan-CK as markers typically associated with chordomas. Tumor cells were negative for GFAP and well-delineated from GFAP positive brain tissue, the findings that were consistent on both analyses. At the time of the first histopathologic diagnosis, the pathology laboratory did not have D2-40 staining. Back then, based on the mor-

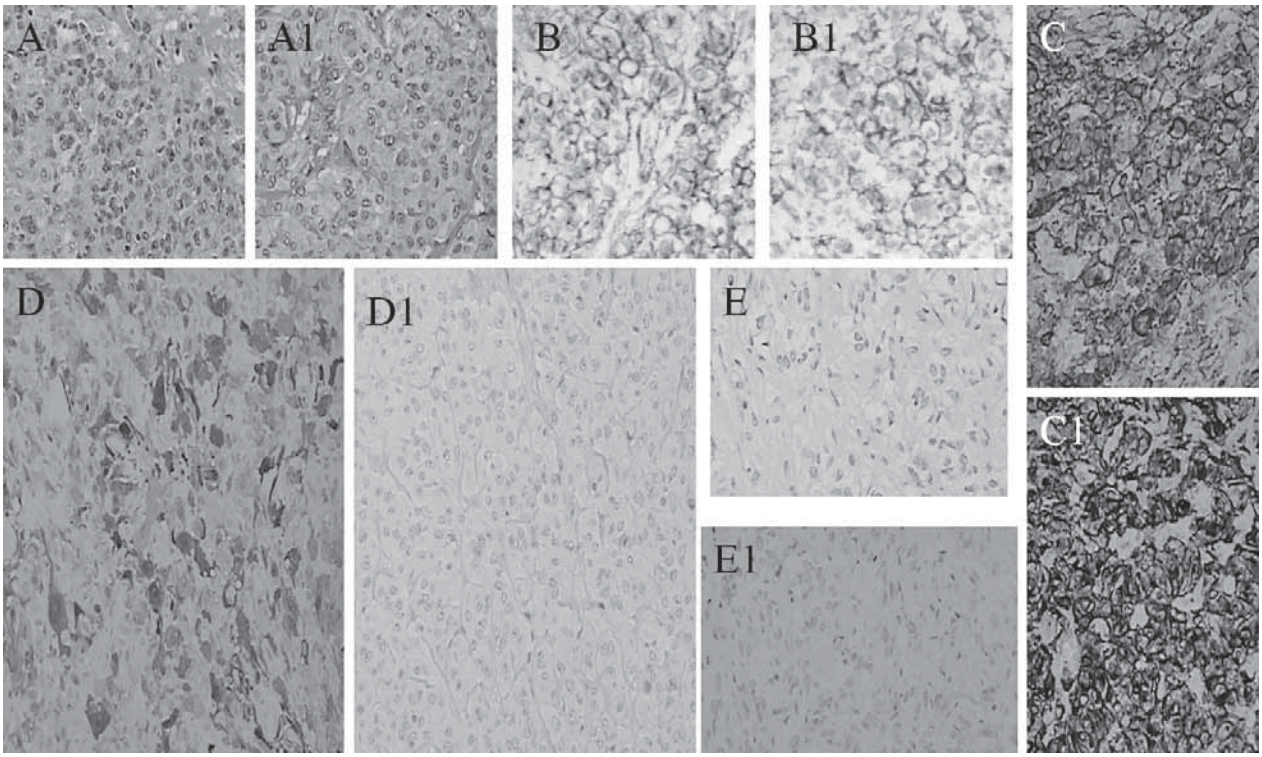

Fig. 6. *The morphological and immunohistochemical study of the tumor tissue acquired at first (A (hematoxylin and eosin stain), B (D2-40), C (epithelial membrane antigen marker), D (S100 protein marker), E (glial fibrillary acidic protein) and second (A1,B1,C1, D1, E1) surgery show a tumor composed of moderately polymorph cells in diffuse or lobular pattern separated by fibrous septa of varying thickness. The cells are embedded in abundant basophilic alcian blue positive mucinous matrix. The cells have oval eccentric nuclei with a dense chromatin pattern. Some cytoplasm contains vacuoles of various size and other cells have a more solid eosinophilic PAS positive cytoplasm. The tumor has areas of pleomorphic cells. The calcification and hemorrhage are uncommon. Tumor cells were positive for epithelial membrane antigen EMA, cytokeratin, VIM and D2-40. Immunostaining for GFAP was negative. Ki-67 in both tumors was 3%. The tumor was well-demarcated from the surrounding brain tissue. Described morphological and immunohistochemical features were found at first and second analysis. The final diagnosis of chordoid meningioma was established based on immunohistochemical positivity for D2-40 and loss of S-100.*

Table 1. *Immunohistochemical profiles of morphologically similar tumors*

	EMA	VIM	pan-CK	GFAP	S-100	D2-40
Chordoma	+	+	+	-	+/-	-
Chondrosarcoma	-	+	-	-	+	+
Myxopapillary ependymoma	-	+	-/+	+	+/-	+/-
Chordoid meningioma	+	+	-/+	-	-	+/-
Our case, first analysis	+	+	+/-	-	+	+
Our case, second analysis	+	+	+/-	-	-	+

phological and immunohistochemical findings, the diagnosis of chordoma was established. The second analysis showed sporadic and very weak S-100 positivity together with positivity for D2-40 staining. Based on the morphological and new immunohistochemical results, a conclusion that it was not a chordoma but a CM was made (Fig. 6 and Table 1).

Couce *et al*. showed that a small portion of CM can be focally positive for S-100 and cytokeratin markers; the majority of CM are lacking S-100 and all

Table 2. *Patients with chordoid meningioma under 18 years of age*

Case	Age (yrs), sex	Localization	Systemic disease	Author, year [reference]	Follow up (years (y), months (m)	Treatment, outcome	Recurrence
1	15, M	Left tentorial	Castelman's disease	Kepes *et al*. 1988	5 y	GTR	No
2	10, M	Right parietal	Castelman's disease	Kepes *et al*. 1988	3 y	GTR	No
3	18, F	Right parietal	Castelman's disease	Kepes *et al*. 1988	2 y	GTR	No
4	17, M	Falx and right parietal	Castelman's disease	Kepes *et al*. 1988	3 y	GTR	No
5	16, F	Falx left occipital	Castelman's disease	Kepes *et al*. 1988	20 m	GTR	Yes
6	8, F	Falx, left	Castleman's disease	Kepes *et al*. 1988	6 m	GTR	No
7	15, F	Tentorial	Previously treated for Wilms tumor	Glasier *et al*. 1993	Not described		
8	10, F	Supratentorial	No	Zuppan *et al*. 1994	Not described		
9	5, M	Bilateral frontal	No	Kumar *et al*. 1996	6 m	GTR	Yes
10	15, F	Right Falco-tentorial	No	Kobata *et al*. 1998	5 y	GTR	No
11	12, F	Fronto-parietal	No	Couce *et al*. 2000	Lost to follow up	GTR	Lost to follow up
12	15, M	Fronto-temporal	No	Couce *et al*. 2000	Lost to follow up	GTR	Lost to follow up
13	12, M	Cerebellum (midline)	No	Epari *et al*. 2006	3 m to 2 y	GTR	No
14	17, M	Cerebellum	No	Epari *et al*. 2006			
15	18, F	Left parietal	No	Epari *et al*. 2006			
16	12, F	Frontal with spinal dissemination	No	Mullassery *et al*. 2006	14 m	GTR, 2 mt follow up, GRT cranio-spinal RT, spinal dissemination after 14 months	Yes
17	3, M	Foramen magnum	No	Marhx-Bracho *et al*. 2007	10 m	GTR	No
18	12, M	3rd ventricle	No	Song *et al*. 2008	12 m	GTR	No
19	11, M	Lateral ventricle (trigonum)	No	Nambiar *et al*. 2012	6 m, 56 m	GTR, GTR and 3D RT	Yes
20	M, 11	3rd ventricle	No	Present case	22 m, 14 m	GTR 22 m, GTR 14 m	Yes

CM were positive for VIM (4). In their series, Cho *et al*. showed that neither one diagnosed chordoma nor all diagnosed CM were positive for S-100, whereas all CMs were negative for pan-CK (3). Huse *et al*. suggest D2-40 immunoreactivity as a useful marker when differentiating CM from chordoma (9). Later studies dealing with immunohistochemical differences between CM and chordoma

showed no significance in D2-40 positivity, and suggested further studies (3) (Table1).

To the best of our knowledge, 19 cases of CM in pediatric population are reported in the literature (Table 2) (16,17,22). The reported CMs were situated supratentorially. In two cases, tumors were reported intraventricularly, i.e. in the lateral ventricle (17) and third ventricle one each (22). The follow up ranged from 3 months to 5 years. There are four cases where tumors recurred after gross total resection. In twelve reported cases, tumors were not associated with systemic disease.

CONCLUSION

This is the second case of CM situated in the third ventricle, and 20th case of CM in the pediatric population. Presented symptoms were not specific and systemic disease was not diagnosed. The tumor was approached transcallosally and interforniceally, and completely removed. Twenty-two months after complete tumor resection, recurrence was confirmed (Fig. 4). Reoperation was performed in the same manner and the tumor was completely removed (Fig. 5).

Histologic and immunohistochemical results showed chordoid and meningeal formations that were GFAP, AC, CHG and HMB45 negative and positive for EMA, VIM, AE1/AE3 and D2-40. S-100 was positive on the first but negative on second analysis (Fig. 6). The first diagnosis was chordoma and the second one CM. Today, the patient attends regular school and is back to his everyday activities. Regular MRI and neurosurgical follow ups 14 months after the second surgery showed no signs of tumor recurrence.

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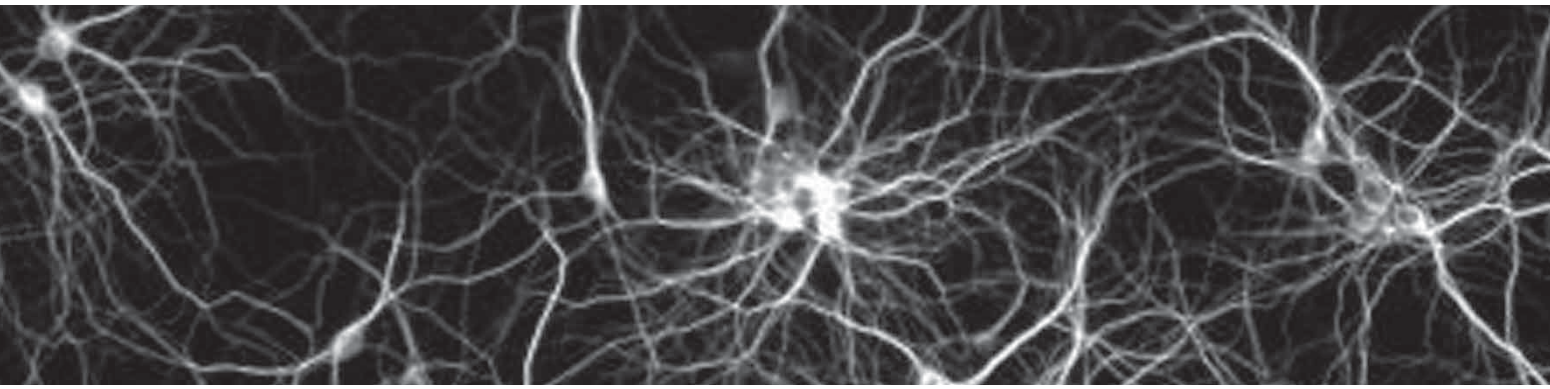
Hordoidni meningeom treće mozgovne klijetke ili hordom: dijagnostička dilema temeljena na jednom slučaju

SAŽETAK - Svrha ovoga rada je predstaviti slučaj i diferencijalnu dijagnostičku dilemu u djeteta s rijetkim tumorom histoloških karakteristika hordoma i hordoidnog meningeoma smještenog u trećoj mozgovnoj klijetki. *Opis slučaja:* Trinaestogodišnjem dječaku dijagnosiciran je recidivni intraventrikularni tumor 22 mjeseca nakon potpunog kirurškog uklanjanja. Indicirana je ponovna operacija te je učinjena ponovna histološka i imunohistokemijska analiza tumora, a bolesnik se nastavio redovno pratiti. Napravljen je pregled literature koristeći ključne riječi: MESH "Cerebral Ventricle Neoplasms" AND "Pediatrics". Histološka i imunohistokemijska analiza nakon prve operacije pokazala je hordom, a nakon druge histološke i dodatne imunohistokemijske analize koja je pokazala pozitivitet na D2-40 marker koji je negativan kod hordoma, a pozitivan kod hordoidnih meningeoma, zaključeno je da se radi o hordoidnom meningeomu. Četrnaest mjeseci nakon ponovljene operacije nije se pokazao recidiv tumora. Literaturni pregled pokazao je dva pedijatrijska slučaja intraventrikularnih hordoidnih meningeoma. Jedan od njih bio je smješten u lateralnoj, a drugi u trećoj mozgovnoj klijetki. *Zaključak:* Ovo je drugi prijavljeni slučaj hordoidnog meningeoma smještenog u trećoj mozgovnoj klijetki u pedijatrijskog bolesnika. U ovom slučaju bolesnik je redovito praćen 22 mjeseca nakon prve operacije i potpunog uklanjanja tumora kada je uočen recidiv tumora. Prva imunohistokemijska analiza pokazala je da se radi o hordomu, a druga je analiza pokazala da se radi o hordoidnom meningeomu. Četrnaest mjeseci nakon druge operacije nije došlo do recidiva. Dječak se vratio svojim svakodnevnim aktivnostima uz hormonsku nadomjesnu terapiju.

Ključne riječi: intraventrikularni meningeom, hordoidni meningeom, pedijatrija, hordom, imunohistokemija



Pontine Ménière's syndrome – a mimicker of Ménière's disease?

Jiann-Jy Chen, MD, Dem-Lion Chen[1], Hsin-Feng Chang[2,3]

ABSTRACT - *Objectives:* In one of 131 patients (48 men and 83 women) diagnosed with Ménière's disease at a neuro-otological clinic over a two-year period, the lesion was localized in the pons rather than the inner ear; herein, we report this rare curiosity. *Case description:* A 25-year-old man presented to our emergency department with vertigo and right tinnitus four times during a 5-year period. The clinical course fitted the diagnostic criteria of definite Ménière's disease and neuroimaging results showed no abnormalities. *Results:* A series of neurotologic studies confirmed right side retrocochlear neural hearing loss, marked depression of the optokinetic nystagmus-slow phase (pursuit) velocity in the leftward direction, and marked depression of the optokinetic nystagmus-fast phase (saccade) velocity in the rightward direction. The symptoms could be attributable to right-sided pontine impairment rather than right inner-ear endolymphatic hydrops. *Conclusion:* Currently, no known vertiginous disease could encode the relapsing symptoms of this patient. The pontine Ménière's syndrome might be a variation of pontine transient ischemia attack with caudal pontine tegmentum syndrome or a pathophysiology similar to that of vestibular migraine.

Key words: Ménière's disease; Ménière's syndrome; neural hearing loss; tinnitus; episodic vertigo

INTRODUCTION

Ménière's disease is diagnosed when there is histopathologic evidence of endolymphatic hydrops. Definite Ménière's disease is confirmed with the following 4 criteria: (a) at least two definitive spontaneous episodes of vertigo persisting for at least 20 minutes; (b) pure tone audiometry documented hearing loss on at least one occasion; (c) tinnitus or aural fullness in the affected ear; and (d) exclusion

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of other causes (1). Using the criteria above, 131 persons (48 men and 83 women) were diagnosed with Ménière's disease at a neurotological clinic at a regional hospital in northern Taiwan over a two-year period (2008-2010). They all received the same diagnostic battery, including a history and physical examination, audiometric tests (pure tone audiometry, speech reception threshold, speech discrimination score [SDS] test, short increment sensitivity index [SiSi] test), tympanogram, electronystagmogram (saccade, smooth pursuit, optokinetic nystagmus [OKN] test, bithermal caloric test), extracranial and transcranial color-coded duplex sonography and brain magnetic resonance imaging/angiography. In one 25-year-old patient, the lesion was topographically localized in the pons rather than the inner ear, although the clinical course fitted the diagnostic criteria of definite Ménière's disease and neuroimaging results showed no abnormalities. Herein, we report this curious case.

CASE REPORT

A 25-year-old man presented to our emergency department with vertigo and right tinnitus four times over a 5-year period. The symptoms always remitted spontaneously in 3 or 4 hours, and then he felt dizzy with surrounding leftward tilting for several hours. He weighed 90 kg with a height of 175 cm and body mass index of 29.4 kg/m^2. He did not have hypertension, diabetes mellitus, heart disease, migraine or other systemic disease. He denied drinking alcohol and coffee, smoking, and areca chewing. He denied any familial hereditary disease, except for his mother who had vertigo of unknown etiology. His vital signs, physical and neurological examinations, and mental status were all normal, with the exception of spontaneous horizontal leftward beating nystagmus. His electrocardiogram, blood chemistry, lipid profile and thyroid function tests were all normal.

At presentation in the emergency department with his 4th symptomatic attack, his judgment, orientation, memory, attention, and calculation were all intact. There was no headache, blurred vision, diplopia, dysphonia, aphasia, dysarthria, dysphagia, hemiparesis, hypesthesia/thermanesthesia, dysmetria, abasia or astasia. Extraocular movements and convergence were intact. On straight-ahead gaze, there was spontaneous horizontal leftward beating nystagmus, which was not suppressed by right-, up-, down- or leftward fixation (Fig. 1A). The clinical head-impulse test of the horizontal semicircular canals was normal. Romberg's test and Mann's test showed rightward tilting. Pure tone audiometry showed mild right high-tone hearing impairment (Fig. 1B). His SDS was 85% in the right ear and 100% in the left ear despite a 0% SiSi (1,000~4,000Hz) in both ears. Testing horizontal and vertical saccades and smooth pursuit eye movements revealed no further deficits. However, electronystagmogram showed marked depression of OKN-slow phase (pursuit) velocity in the leftward direction, and poor manifestation of the OKN-fast phase (saccade) velocity in the rightward direction (Fig. 1C). Bithermal caloric tests (warm [47 °C] and cool [27 °C] water, 20 seconds) demonstrated unilateral weakness of -37.5% (Fig. 1D) using Jongkee's formula, explaining right-sided weakness, and all visual suppressions were positive (Fig. 1D). Furthermore, emergency brain magnetic resonance imaging/angiography and extracranial and transcranial color-coded duplex sonography showed no abnormalities.

During the next three years, he experienced four additional episodes of the symptoms and received symptomatic therapy at our emergency department. During the inter-ictal uneventful period, physical examination, audiometric tests, tympanogram, electronystagmogram and bithermal caloric test results were normal.

DISCUSSION

Ménière's disease is frequently considered in the cases of relapsing unilateral tinnitus and vertigo. The symptoms are sometimes caused by an acoustic tumor or vestibular migraine; the former can be diagnosed by neuroimaging and the latter by a history of migraines (2,3). In addition, rotational vertebral artery syndrome (Bow-Hunter syndrome) should be considered if head rotation induces symptoms (4). According to the above criteria, only Ménière's disease might be considered in our patient because his clinical course fulfilled the diagnostic criteria of definite Ménière's disease, the neuroimaging results were normal, and he did not have migraines.

Speech discrimination loss is proportional to cochlear (sensory) hearing loss, whereas it is disproportionately greater in retrocochlear (neural) hearing loss. Use of an SDS test alone cannot discriminate between cochlear (sensory) and retrocochlear (neural) hearing loss. A recruitment test, such as an SiSi test or alternate binaural loudness balancing test, should also be performed (5). In our patient, mild right high-tone hearing impairment

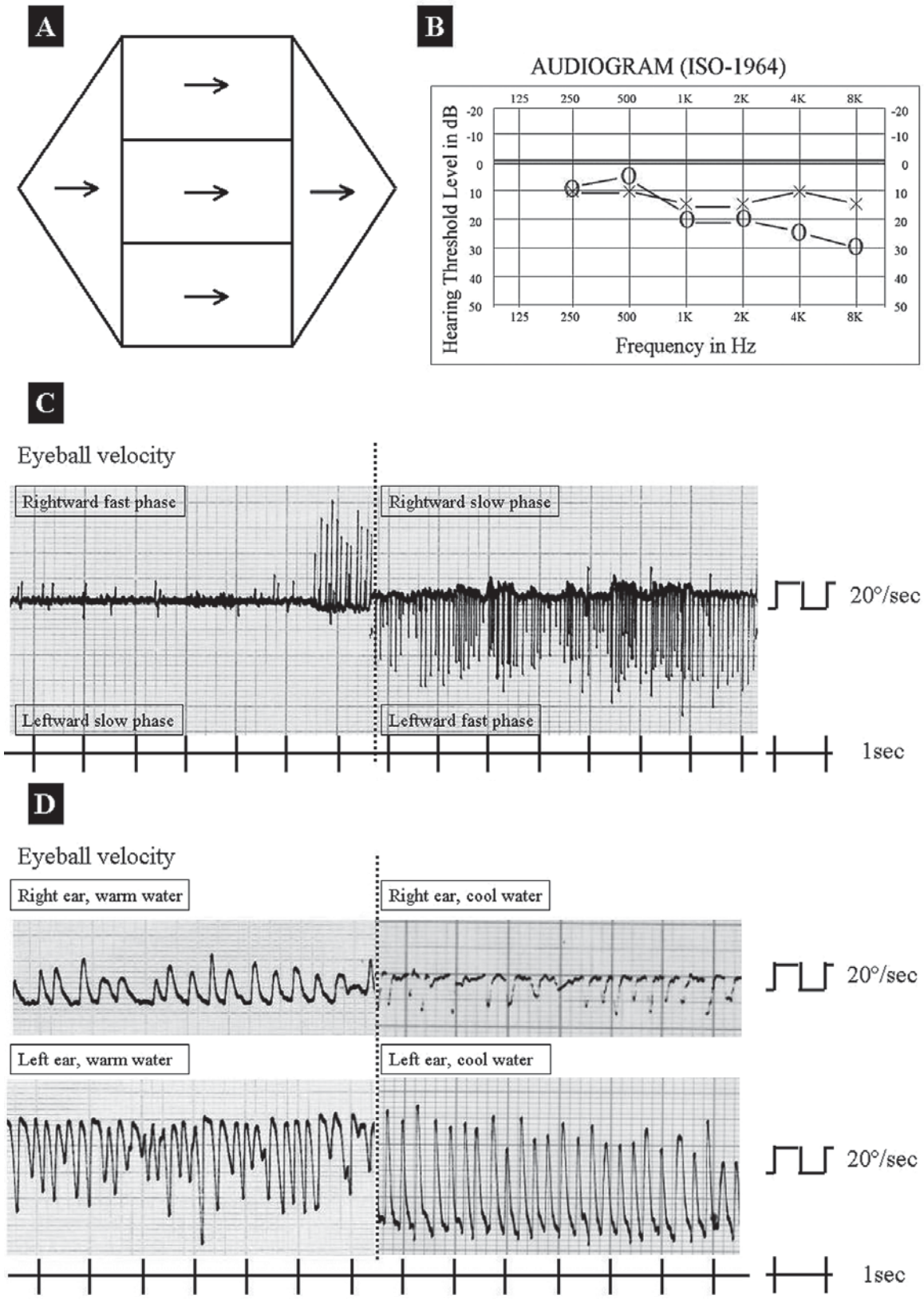

Fig. 1. *(A) On straight-ahead gaze, a spontaneous horizontal leftward beating nystagmus is observed, which is not suppressed by right-, up-, down- or leftward fixation; (B) pure tone audiometry shows mild right high-tone hearing impairment; (C) an optokinetic electronystagmogram shows marked depression of the slow phase (pursuit) velocity in the leftward direction and poor manifestation of the fast phase (saccade) velocity in the rightward direction; (D) bithermal caloric tests shows that maximum slow-phase velocities of warm (47 °C) and cool (27 °C) caloric nystagmus in the right ear are both lesser than those in the left ear.*

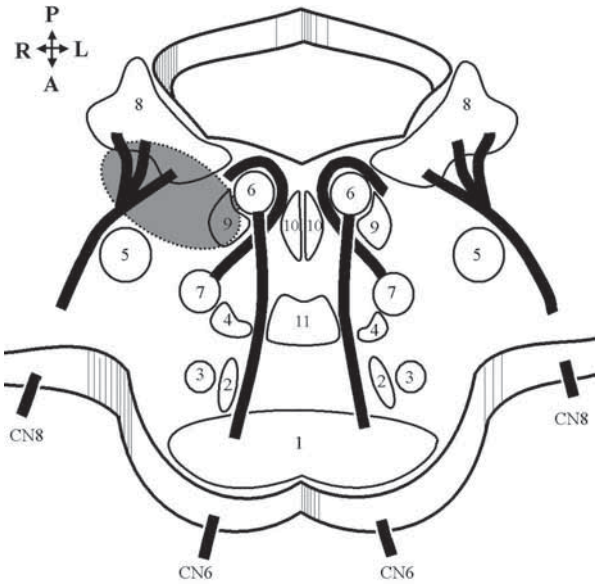

Fig. 2. *The symptoms are attributable to a presumed lesion (gray circle) in the right pontomedullary junction, involving the right vestibular nucleus (No. 8), right paramedian pontine reticular formation (No. 9) and right auditory nerve (CN 8). No. 1: corticospinal tract; No. 2: lateral spinothalamic tract; No. 3: rubrospinal tract; No. 4: lateral lemniscus; No. 5: trigeminal spinal tract; No. 6: abducens nucleus; No. 7: facial nucleus; No. 10: medial longitudinal fasciculus; No. 11: trapezoid body; CN 6: abducens nerve and fasciculus.*

with a 0% SiSi excluded hearing symptoms of cochlear origin, and the right-sided 85% SDS indicated a retrocochlear (neural) lesion of the right auditory nerve with ipsilateral neural hearing loss when he was symptomatic.

A directional preponderance of the OKN-slow phase (pursuit) velocity was found corresponding to spontaneous nystagmus. Unilateral peripheral vestibular hypofunction results in enhancement of the nystagmus OKN-slow phase (pursuit) velocity toward the side of the lesion and depression of the OKN-slow phase (pursuit) velocity toward the opposite horizontal direction (6). Theoretically, unilateral Ménière's disease with ipsilateral vestibular hyperfunction results in spontaneous nystagmus toward the lesion side, consisting of the fast phase toward the lesion side and slow phase toward the opposite side. Hence, patient with unilateral Ménière's disease should have depression of the OKN-slow phase (pursuit) velocity toward the lesion side and enhancement of the OKN-slow phase (pursuit) velocity toward the opposite horizontal direction. In our patient, right peripheral vestibular hypofunction on bithermal caloric tests and marked depression of the OKN-slow phase (pursuit) velocity in the leftward direction were explained by right peripheral vestibular hypofunction.

If extraocular movements are intact and there is no double vision, the horizontal pursuit and horizontal saccade tests focus on dysfunction of the ipsilateral paramedian pontine reticular formation (PPRF) (paraabducens nucleus or nucleus praepositus XII). The OKN test magnifies dysfunction of the ipsilateral PPRF if no parietal lobe lesion is found on neuroimaging (7). The bithermal caloric nystagmus test focuses on ipsilateral peripheral vestibular function and the visual suppression test focuses on the ipsilateral cerebellar flocculonodular lobe (8). In our patient, the poor manifestation of the OKN-fast phase (saccade) velocity could be explained by impairment of the right PPRF, representing ipsilateral central vestibulopathy. In addition, because of the leftward spontaneous nystagmus and right peripheral vestibular hypofunction, concomitant right peripheral vestibulopathy was considered. The bilateral positive visual suppression test showed that both cerebellar flocculonodular lobes were normal. Eventually, the episodic symptoms could be attributable to right-sided pontine impairment (Fig. 2) rather than ipsilateral inner-ear endolymphatic hydrops

CONCLUSION

The right retrocochlear (neural) hearing loss, impairments of OKN and ipsilateral peripheral vestibular hypofunction were not compatible with the pathophysiology of Ménière's disease. Besides, pure horizontal nystagmus is usually not found in a peripheral vestibular failure, and might indicate a central origin. Hence, our patient's symptoms were attributable to one-sided pontine impairment despite the normal neuroimaging results. Currently, no known vertiginous disease could encode our patient's relapsing symptoms. The pontine Ménière's syndrome might be a variation of pontine transient ischemia attack with caudal pontine tegmentum syndrome or a pathophysiology similar to that of vestibular migraine (9). The novel vertiginous disease herein might masquerade as Ménière's disease in most patients, with an incidence of 0.8% (1 of 131) among those fitting the diagnostic criteria of definite Ménière's disease.

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Ménièreov sindrom na ponsu – oponašatelj Ménièreove bolesti?

SAŽETAK – U jednog od 131 bolesnika (48 muškaraca, 83 žene) kojima je u jednoj neurološkoj klinici u razdoblju od više od dvije godine postavljena dijagnoza Ménièreove bolesti lezija je bila lokalizirana u ponsu, a ne u unutarnjem uhu. Slučaj bolesnika opisujemo zbog rijetkosti. Dvadesetpetogodišnji muškarac došao je u naš hitni odjel 4 puta s vrtoglavicom i tinitusom desnog uha u razdoblju od preko pet godina. Klinički tijek je odgovarao dijagnostičkim kriterijima nedvojbene Ménièreove bolesti, a rezultati neuroslikovne pretrage nisu pokazivali nenormalnosti. Niz neurotoksikoloških studija potvrdio je neuralni gubitak sluha desno retrokohlearno, izraženu depresiju brzine sporofaznog optokinetičkog nistagmusa u smjeru lijevo i izraženu depresiju brzofaznog optokinetičkog nistagmusa (sakadni) u smjeru desno. Simptomi bi se mogli pripisati više desnostranom oštećenju ponsa nego endolimfatičkom hidropsu desnog unutarnjeg uha. Zaključuje se da se danas nijedna poznata vrtoglavica ne bi mogla pripisati ponavljajućim simptomima tog pacijenta. Ménièreov sindrom ponsa mogao bi biti varijacija prolazne ishemijske atake u ponsu s kaudalnim sindromom tegmentuma ponsa ili patofiziološka promjena slična vestibularnoj migreni.

Ključne riječi: Ménièreova bolest, Ménièreov sindrom, neurološki gubitak sluha, tinitus, epizodni vertigo

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4. **Izvještaji o slučajevima Klinike za neurologiju Kliničkog bolničkog centra Zagreb** će biti zatraženi od strane urednika.
5. **Slike u neurologiji**: Namjena ove kategorije je da prikaže vizualnu sliku zanimljivog i jedinstvenog neurološkog opažanja. Slike pacijenata zajedno sa slikama provođenja dijagnostičke procedure su dobrodošle. Maksimalna duljina: 200 riječi za opis slučaja, 50 riječi za svaku sliku, maksimalno dvije reference.
6. **Pisma uredniku**: Pisma koja raspravljaju o nedavnom članku objavljenom u časopisu *Neurologia Croatica* su dobrodošla. Pisma trebaju biti primljena unutar 3 mjeseca od objave članka. Kratki komentari o aktualnim pitanjima koja su od javnog interesa su također mogući. Maksimalna duljina: 500 riječi (uključujući sav tekst, opise slike i literaturu).

Uz navedene tipove objavljuju se i najave/izvješća profesionalnih i znanstvenih okupljanja.

Autorska izjava. Autorska izjava je obrazac koji možete preuzeti na svom računalu s web stranice časopisa: http://www.neurologiacroatica.com/en/InstructionsForAuthors.html **Ovaj obrazac treba ispuniti i potpisati glavni autor teksta, skenirati i poslati elektroničkom poštom zajedno s tekstom**. Svi tekstovi bez potpisane autorske izjave će biti vraćeni autoru.

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Sažetak ne treba imati više od 250 riječi. Izvorni znanstveni radovi trebaju imati strukturirani sažetak sa slijedećim naslovima: ciljevi, metode, rezultati i zaključci. Sažeci za neurološke preglede trebaju biti nestrukturirani. Izvještaji o slučajevima trebaju imati strukturirane sažetke sa slijedećim naslovima: ciljevi, opis slučaj, rezultati, zaključak. Slike u neurologiji i pisma uredniku ne zahtijevaju sažetak. U njemu valja navesti samo glavne rezultate, a izbjegavati općenite opise i poznate činjenice. Iza sažetka treba abecednim redom navesti tri do deset ključnih riječi. Molimo da ključne riječi potražite preko linka MeSH Database na web stranici http://www.ncbi.nlm.nih.gov/pubmed/.

Tekst rada treba, ako je prikladno, podijeliti u dijelove: Uvod, Materijal i metode, Rezultati, Rasprava i Zaključak. Znanstveni radovi, uključujući literaturu, ne bi trebali prelaziti 12 stranica (32 retka od 60 slovnih mjesta na stranici), a kratka priopćenja 3 stranice.

Tablice trebaju biti svaka na posebnoj stranici. Fotografirane tablice nisu prihvatljive. Ilustracije se prilažu u obliku prikladnom za reproduciranje. Rukom rađeni crteži, laboratorijski materijal, npr. ispisi, rentgenogrami i sl., šalju se u obliku crno-bijelih fotografija, veličine do 20x25 cm. Ako su prilozi u boji (tablice, fotografije i sl.), autor snosi trošak tiskanja te stranice u dogovoru s tiskarom "Denona". Za svaku fotografiju na kojoj se bolesnik može prepoznati potrebna je pismena privola. Na poleđini svake slike valja označiti njezin broj i vrh. Usto, na primjercima ilustracija priloženim uz glavni primjerak teksta treba na poleđini navesti ime prvog autora. Autori trebaju voditi računa o mogućoj potrebi smanjivanja ilustracija. Tablice i slike valja označiti arapskim brojevima redom njihova spominjanja u tekstu. Opis svake od njih treba biti tipkan na posebnom listu papira. Broj slika ne bi trebao biti veći od 6.

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Časopisi

Treba navesti sve autore ukoliko ih je šest ili manje: Mubrin Z., Kos M. Assessment of dementia. Flow chart approach to clinical diagnosis. Neurol Croat 1992; 41: 141-156.

Ako citirani rad ima sedam ili više autora, treba navesti samo prva tri autora i dodati *et al*.

Baršić B, Lisić M, Himbele J *et al*. Pneumococcal meningitis in the elderly. Neurol Croat 1992;41:131-140.

Knjige

Critchley M. The ventricle of memory. New York: Raven Press, 1990.

Poglavlje u knjizi

Geschwind N. The borderland of neurology and psychiatry: some common misconceptions. In: Bensom DF, Blumer D, eds. Psychiatric aspects of neurologic disease. New York: Grune and Stratton, 1975:1-9.

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