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Case Report / Приказ случаја

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Diagnostic dilemmas of Rasmussen's encephalitis in adults

Дијагностичке дилеме код Расмусеновог енцефалитиса одраслих

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SUMMARY

Introduction Rasmussen's encephalitis (RE) represents a rare, progressive and inflammatory disease of the brain. Its detection in adults is a great challenge in clinical medicine.

The aim of this paper is to highlight the diagnostic dilemma of RE in adult.

Case report A 46-year-old woman was hospitalized due to stubborn diffuse intense headaches followed by nausea and urge for vomiting that makes her wake up during the night. On several occasions she had transitory speech and memory disorders, and right hand numbness. MR findings: occipitoparietal left in the deep white matter, as well as subcortical T2/flair white matter hyperintensities, T1-hypointense change that involves the corpus callosum. MR spectroscopy shows increased level of choline / creatinine (Cr) (2.12), reduction of N-acetylaspartate / Cr (1.27), increased level of myo-inositol / Cr (1.20) and the presence of lactate. The patient refused lumbar puncture. Due to the described changes close to speech center, cerebral biopsy was not taken. Even after 5 years MR and spectroscopic findings are unchanged while clinical condition remained stable and unchanged.

Conclusion This case highlights the diagnostic dilemmas that arise in adult-onset RE and suggests that this diagnosis should be considered in patients of any age with an appropriate clinical picture.

Keywords: Rasmussen's encephalitis; adult; diagnosis, diferential; encephalitis, diagnosis

САЖЕТАК

Увод Расмусенов енцефалитис (РЕ) је ретко, прогресивно, инфламаторно обољење мозга које је тешко доказати у одраслих особа.

Циљ овог рада је да истакне дијагностичке дилеме код РЕ одраслих.

Приказ болесника Жена стара 46 година, хоспитализована је због упорних дифузних, интензивних главобоља, праћених мучнином и нагоном на повраћање, због којих се будила ноћу. Више пута је имала транзиторни поремећај говора и памћења и утрнулост десне руке. МР налаз: окципитопаријетално лево у дубокој белој можданој маси као и субкоритикално уочава се *T2/flair* хиперинтензна, Т1 хипоинтензна промена која захвата *corpus callosum*. Спектроскопски се евидентира повишена вредност односа холин / креатинин (Кр) (2.12), редукован ниво азот-ацетил-аспартата (НАА) / Кр (1.27), повећана вредност мио-инозитола / Кр (1.20) и присуство лактата. Болесница је одбила лумбалну пункцију. Због близине описане промене и центра за говор није урађена биопсија мозга. После пет година, МР и спектроскопски налази су непромењени, а стање болеснице стабилно.

Закључак Овај случај наглашава дијагностичке дилеме код РЕ одраслих РЕ и указују на то да ову дијагнозу треба узети у обзир код пацијената било којег узраста са одговарајућом клиничком сликом.

Кључне речи: Расмусенов енцефалитис; одрасли; дифернецијална дијагноза; енцефалитис, дијагноза

INTRODUCTION

Rasmussen's encephalitis (RE) represents a rare, progressive and inflammatory disease of the brain. Its detection is a great challenge in clinical medicine. It is usually asspciated with intractable motor seizures, mainly focal seizures, epilepsia partialis continua (EPC), and progressive cognitive impairment with hemiparesis as well as with language and cognitive disorders [1].

The disease was originally described by Theodore Rasmussen et al. in 1958 in the article entitled Focal seizures due to chronic localized encephalitis [2]. According to the author's opinion the first RE attack most frequently occurs during childhood period between 1st and 11th year of life in previously healthy children. Forty years later, cases of chronic encephalitic epilepsy in adults and adolescents, independent of gender, were presented as RE variants [3]. The oldest patient presented in the literature was a 54-years-old female from Australia [4].

The greatest enigma connected with RE is the etiological basis of the disease. The most recent attempts in the identification of pathogenic viral agents are incomplete and contradictory. A great number of researches involves the identification of antibodies responsible for the development of RE.

In 1944 Rogers et al. published a hypothesis that the major etiological role has the antibody against glutamate/AMPA subunit 3 receptor (GluR3). This theory is based on the fact that rabbits vaccinated with GluR3 antibodies show similar clinical features as patients with RE [5]. However, neither GluR3 nor other antibodies have been detected in all RE patients and are not strictly specific for RE only, but could be also found in other types of severe epilepsies. Today, autoimmune hypothesis of RE is increasing more often represented due to transitory efficiency of plasmapheresis [6] or other immunomodulatory drugs in the RE treatment. Attempts to prove genetic cause of this disease were also unsuccessful. In contrast from its unclear etiology, there are four various pathogenic forms defined by brain biopsy finding [7].

Diagnosis is based on EEG, MRI findings, as well as on clinical and/or histological characteristics. In 2005 European consensus group [8] suggested diagnostic criteria for RE (Table 1).

Table 1. Diagnosis criteria according to European consensus statement [8].

RE can be diagnosed if either all three criteria of Part A or two out of three criteria of Part B are present.		
Part A	1. Clinical 2. EEG 3. MRI	Focal seizures (with or without epilepsia partialis continua) and Unilateral cortical deficit(s); Unihemispheric slowing with or without epileptiform activity and Unilateral seizure onset; Unihemispheric focal cortical atrophy and at least one of the following: Grey or white matter T2/FLAIR hyperintense signal Hyperintense signal or atrophy of the ipsilateral caudate head
Part B	1. Clinical 2. MRI 3. Histopathology	Epilepsia partialis continua (EPC) or Progressive unilateral cortical deficit(s) Progressive unihemispheric focal cortical atrophy T cell dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules) and reactive astrogliosis. Numerous parenchymal macrophages, B cells or plasma cells or viral inclusion bodies exclude the diagnosis of RE.

Evaluation of the disease requires neuroimaging such as positron emission tomography (PET), single photon emission tomography (SPECT) or spectroscopy magnetic resonance imaging (sMRI). The quoted methods are inevitable in the diagnostics and follow-up of RE.

The aim of this paper is to highlight the diagnostic dilemma associated with RE in adult.

CASE REPORT

A 46-year-old female, right-handed, hospitalized at the Institute for Neurosurgery due to headaches followed by nausea and urge for vomiting which keeps her awake at night. The disease onset occurred with the patient in full health, after a three-day subfebrile temperature (37.1°C). During the last 2 months she experienced everyday diffuse headaches rated 9-10/10. Pain began from the dorsal aspect of the head left with propagation toward apex and resistant to analgesic therapy. Beside headache she also experienced vertigo and unsteady gait followed by movement to the left. She had frequent short-lasting numbness of the right hand and transitory dysphasic problems: impossible to either correctly pronounce a started sentence or to remember it later. She dismissed head injury on birth or during life-time. Family history of stroke, smoker for twenty years (20 cigarettes per day).

Physical findings: conscious, afebrile, actively movable, psychically unremarkable, of normal vital parameters (blood pressure, heart frequency), internistic, neurological and ophthalmological findings are within the normal limits). The patient underwent transcranial Doppler of cerebral blood vessels, electroencephalography, echocardiography, electrocardiography, heart and lungs radiography, blood analyses (glycemia, electrolytes, total blood count with thrombocytes, prothrombine (INR) and partial thromboplastine time, lipid status, renal and liver functions, tests for thrombophylia, hormone level in blood). All findings were within normal limits. Head computed tomography (CT) scan: suptraventricuarly parietally left, axially a smaller zone of ischemically changed brain parenchyma /SEQ 17 et 18/. Normal electroencephalogram (EEG) activity.

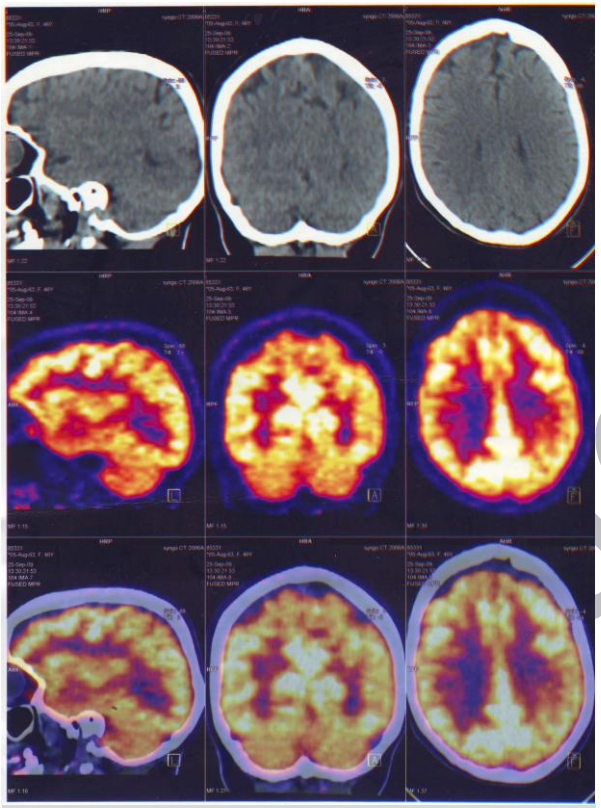

Figure 1. PET/CT finding.

PET/CT (Positron Emission Tomography/ Computed Tomography) finding (Figure 1): in the projection of the periventricular brain white matter paryetooccipitally left intensive accumulation of fluorodeoxyglucose as compared to the level of accumulation in brain structures contralaterally at the analogue level. Hypermetabolic zone of this white matter region can correspond differentially-diagnostically to a benign lesion feature, however, the possibility of the presence of a low-grade tumor lesion (glial TU) cannot be either excluded with absolute security.

Magnetic resonance (MR) was performed with endocranial spectroscopy as well as angiography of intracranial blood vessels. Sagittal TIW, T2W transversally, FLAIR transversally and T2W coronary of the head were also performed as well as multivoxel MR spectroscopy of the pathologic process of cerebral left hemisphere and corresponding location of the right hemisphere. Parieto-occipitially left deep in the white matter of the brain, as well as subcortically, T2/flair hyperintensive, T1 hypointense change involving the corpus callosum splenium of the left side can be visualized (Figure 2). There is a mild atrophy of the left lateral horn but without either strong effect on the surrounding cerebral parenchyma, diffusion restriction

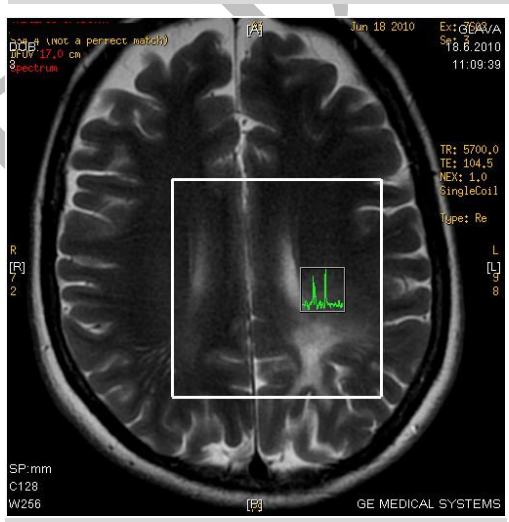

Figure 2. MR finding.

or increased post-contrast. In the surrounding region there are signs of occipitoparietal atrophy. There are stained non-specific lesions in the parietal subcortex right and stained microvascular ischemic lesions in the medial aspect of the right thalamus. Sulcuses at the convexity are mildly expanded in the interparietal segment bilaterally and peri-lesionally. The cerebral cortex and two hemispheres are without any pathological changes. Orbits are without pathological changes. VII to VIII nerve complex are bilaterally of normal pathological form. The foramen magnum is free.

Spectroscopically, inside the pathological process there is the increased level in the relation choline (Cho)/creatinine (Cr) [2], reduction (1.27), N-acetyl-aspartate (NAA) / Cr increased level of myo-inositol (mIno) / Cr (1.20) and the presence of lactate (Figure 3).

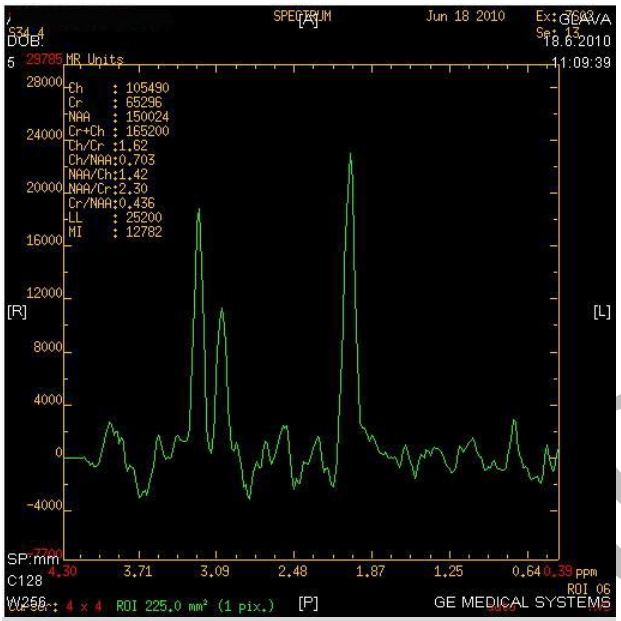

Figure 3. Spectroscopically finding.

As concluded, the pathological process of the supratentorial white matter of the parietal segment according to MR characteristics corresponds to inflammatory/post-inflammatory sequels. Having in mind the focal perilesional atrophy and the existing suspected RE, examination of liquor in order to confirm the presence of positive oligoclonal answer was suggested. However, the patient refused lumbar puncture. Due to the described change close to speech center, cerebral biopsy was not taken. The decision of the Neurosurgical Consilium is that at the time there were no indications for surgical intervention. The patient was released with antiepileptic and antidepressant therapy. Follow-up MRI performed at 6 months, 1 year, and 5 years. Even after 5 years MRI and spectroscopic findings are unchanged while clinical condition remained stable and unchanged. The dilemma is: Is this adult-onset Rasmussen's encephalitis?

DISCUSSION

In about 10% of cases RE onset occurs only after age 37 years as in the presented case [3]. This chronic, progressive inflammatory disease most often involves only one cerebral hemisphere, left in our patient. Several clinical and electrophysiological studies suggest bilateral cerebral involvement with e.g. mild contralateral atrophy [8, 9].

Regardless of innovations in the domain of medicine, even after 50 years since RE discovery, etiology of this disease has remained unclear. Three hypotheses have been forwarded: (a) a direct viral insult, (b) an autoimmune process triggered through a viral agent, (c) a primary autoimmune process. The first and the second hypotheses have been confirmed by case reports of patients with minor infections before disease onset (our patient was subfebrile [9]. Lately, three phases of the disease have

been described: *prodromal phase* lasting 0-8.1 years, *acute phase* with manifested symptoms of the disease (seizures, neurological disorders: hemiparesis, hemianopia, disorders of cognitive functions and speech disorders) [10] of the average duration of 8 months, as in our patient, and the third, *residual phase* with the stabilization of condition with variable duration.

Based on the suggested diagnostic criteria for RE of the European Consensus Group, presented in the Table 1, our patient has fulfilled two of three criteria in part A: 1. Clinical: symptoms of a simple partial attack (speech disorder, i.e. nominal dysphasia and memory disorder, hand numbness, without loss of consciousness) and one-sided cortical deficit (occipitoparietal left), 2. MRI: occipitoparietal left in the deep cerebral matter and subcortically T/2flair hyperintensive change, ipsilateral atrophy is visualized. Oguni et al. [10] quantified clinical types of attacks (clinical seizure types) during the disease. According to the authors, simple partial attacks involving one side of the body are most frequent (in about 77% of cases). There are scientific proofs that ECG can contribute to making diagnosis of RE already in the early phase of the disease [9].

Serial MRI findings of several patients have been published during the last years. The opinion of the Italian group [11] is that MRI demonstrates progression of RE and can suggest diagnosing the disease in the early phase, often before the onset of neurological deficite. PET and SPECT are usually used in the late phase and do not give concrete results. Early RE diagnosis is crucial in the selection of patients who require aggressive medicamentous therapy or surgical intervention such as hemispheroctomy.

According to the Montreal group (Rasmussen et al., 1958; Rasmussen and Andermann, 1989) [12,13] standard cerebrospinal fluid tests (CTF) are not reliable for the confirmation or rejection of RE diagnosis. Serological CTF tests are usually applied in order to exclude infections by well-known neurotropic viruses. Our patient refused lumbar puncture. In most cases PET method detects large hypometabolic zones of the involved hemisphere, while new zones with focal hypermetabolism are found in somewhat lower number [11,14]. Lee has proposed that PET may guide brain biopsy in cases with inconclusive or normal MRI findings, especially in early stages [15]. Magnetic resonance spectroscopy (MRS) investigation indicates that lowering the level of N-acetil-aspartate (NAA) and increasing (or normal) levels of choline (Cho) results in the increased relation NAA/Cho that indicates the loss of dysfunction [9]. Increased level of present lactates as in our case is associated with the presence of EPC. Therefore, PET, SPECY and MRS techniques are not adequate for defining inflammatory nature of RE. They can be helpful in the confirmation of the unihemispheric nature in the early phase of suspected RE. Cerebral biopsy is not necessary in all REs because other criteria can be could be sufficient in making diagnosis (Table 1).

Corresponding tests should be applied to confirm RE and exclude other diseases. Most frequently used cerebral scans are MR, SPECT and if necessary fluorodeoxyglucose positron-emission tomography PET scans. Next, blood tests for exclusion of infection, lumbar puncture for confirming inflammation and infection, and finally cerebral biopsy to confirm the diagnosis are

necessary to be performed. In our patient differential-diagnostic considerations were aimed at: 1.other unilateral neurologic syndromes (stroke, tumor), 2.other reasons for EPC (drugs, cerebral gliomatosis) or 3.other inflammatory or infectious diseases that mimic RE (vasculitis, multiple sclerosis, viral or toxoplasmosis encephalitis) [9]. Although lumbar puncture has offered response to the question whether there is or isn't the presence of inflammation and cerebral infection, our patient was not willing to undergo the procedure. Although cerebral biopsy is necessary in the absolute diagnostics of RE, due to the described change and speech center, it was not performed in our patient.

After making diagnosis, medicamentous or surgical treatment can be applied. To treat TE antiepileptics alone or in combination with other drugs (as in our case) have only limited effect in the control of focal attacks and EPC. In this case the general rule is that the number and dosage of antiepileptics should be as low as possible, as in our case. Recently, long-term treatments have been attempted with corticosteroids, intravenous immunoglobulins (IVIG), plasma-exchange or Tacrolimus [16]. Only a few patients have been treated with Rituximab as the alternative therapy for RE [17].

Among the first description of diseases, surgical treatment (hemispherectomy) remains the most efficient therapy in the prevention of attack progression caused by RE. In our patient, surgery was not indicated but only MRI follow-up.

This case highlights the diagnostic dilemmas that arise in adult-onset RE and suggests that this diagnosis should be considered in patients of any age with an appropriate clinical picture. Rasmussen's encephalitis in adult can be a challenging diagnosis.

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