

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Diagnostic dilemmas of Rasmussen's encephalitis in adults

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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 adults.

Case outline A 46-year-old woman was hospitalized due to persistent intense diffuse headaches, followed by nausea and the urge for vomiting that made her wake up during the night. On several occasions, she had transitory speech and memory disorders, and right hand numbness. Magnetic resonance (MR) imaging findings were as follows: occipitoparietal left in the deep white matter, as well as subcortical T2/flair white matter hyperintensities, T1-hypointense change involving the corpus callosum. MR spectroscopy showed an increased level of choline/creatinine (Cr) (2.12), a reduction of N-acetylaspartate/Cr (1.27), an 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 the speech center, cerebral biopsy was not taken. Even after five years, MR and spectroscopic findings are unchanged, while the clinical condition remains 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 the appropriate clinical picture.

Keywords: Rasmussen's encephalitis; adult; diagnostic; dilemma

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 associated with intractable motor seizures, mainly focal seizures, epilepsy partialis continua (EPC), and progressive cognitive impairment with hemiparesis, as well as with language and cognitive disorders [1].

The disease was originally described by Rasmussen et al. [2] in 1958. According to the author's opinion, the first RE attack most frequently occurs during childhood period between the first and the 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-year-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. Rogers et al. [5] published a hypothesis that the antibody has a major etiological role 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. However, neither GluR3 nor other antibodies have been detected in all RE patients and are not strictly specific to RE but could also be found in other types of severe epilepsies. Today, autoimmune hypothesis of RE is presented more often due to transitory efficiency of plasmapheresis or other immunomodulatory drugs in the RE treatment [6]. Attempts to prove a genetic cause of this disease were also unsuccessful. In contrast from its unclear etiology, there are four various pathogenic forms defined by brain biopsy findings [7].

Diagnosis is based on electroencephalogram (EEG) and magnetic resonance imaging (MRI) findings, as well as on clinical and/or histological characteristics. Bien et al. [8] (European Consensus Group) suggested diagnostic criteria for RE (Table 1).

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

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

CASE REPORT

We present a case of a 46-year-old female, right-handed, hospitalized at the Institute for Neuro-

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Table 1. Diagnosis criteria according to the European Consensus Statement [8]; Rasmussen's encephalitis 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	1. Focal seizures (with or without EPC) and unilateral cortical deficit(s) 2. Unihemispheric slowing with or without epileptiform activity and unilateral seizure onset 3. 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	1. EPC or progressive unilateral cortical deficit(s) 2. Progressive unihemispheric focal cortical atrophy 3. 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.

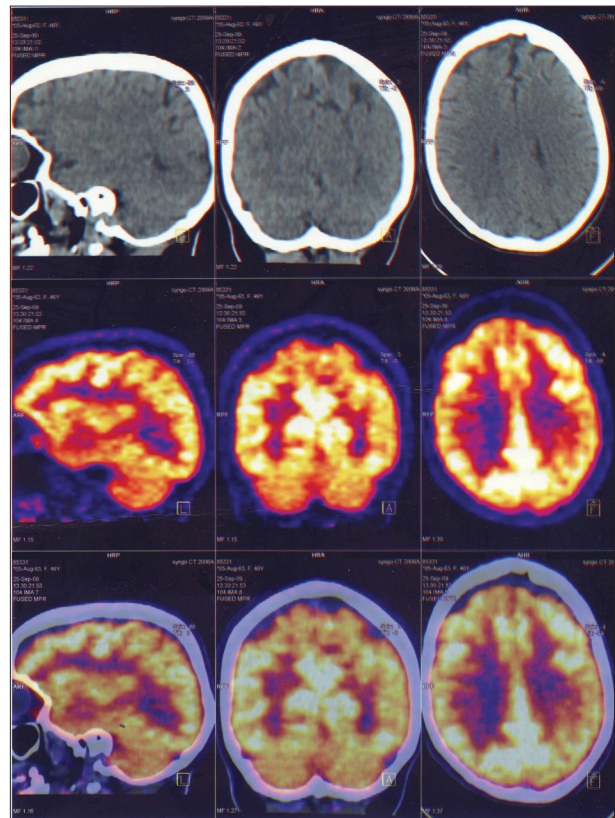
EEG – electroencephalography; MRI – magnetic resonance imaging; EPC – epilepsy partialis continua; RE – Rasmussen's encephalitis

surgery due to headaches followed by nausea and the urge for vomiting which kept 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 previous two months, she experienced everyday diffuse headaches rated 9–10/10. The pain occurred at the dorsal aspect of the head, left, with propagation toward the apex, resistant to analgesic therapy. In addition to the headache, she 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: inability to either correctly pronounce a started sentence or to recall it later. She dismissed head injury on birth or during lifetime. She had a family history of stroke and was a smoker for twenty years (20 cigarettes per day).

Physical findings of the patient were as follows: conscious, afebrile, actively movable, psychically unremarkable, of normal vital parameters (blood pressure, heart frequency), internistic, neurological and ophthalmological findings 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 thromboplastin time, lipid status, renal and liver functions, tests for thrombophilia, hormone level in the blood). All the findings were within normal limits. Head computed tomography (CT) scan revealed supraventricularly parietally left, axially, a smaller zone of ischemically changed brain parenchyma /SEQ 17 et 18/. The EEG activity was normal.

PET/CT (positron emission tomography/computed tomography) finding (Figure 1) was as follows: in the projection of the periventricular brain, white matter parieto-occipitally 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-diagnostics to a benign lesion feature; however, the possibility of the presence of a low-grade tumor lesion (glial TU) cannot be excluded with absolute certainty.

MRI was performed with endocranial spectroscopy, as well as angiography of the intracranial blood vessels. Sagittal TIW, T2W transversally, FLAIR transversally, and T2W coronary of the head were also performed, as well

**Figure 1.** Positron emission tomography/computed tomography finding

as multi-voxel sMRI of the pathologic process of the left cerebral hemisphere and the corresponding location of the right hemisphere. Parieto-occipitally left deep in the white matter of the brain, as well as subcortically, T2/flair hyperintense, T1 hypointense change involving the corpus callosum splenium of the left side could be visualized (Figure 2). There was a mild atrophy of the left lateral horn but without strong effect on the surrounding cerebral parenchyma, diffusion restriction, 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. Sulci at the convexity were mildly expanded in the interparietal segment bilaterally and perilesionally. The cerebral cortex and two hemispheres were without any pathological

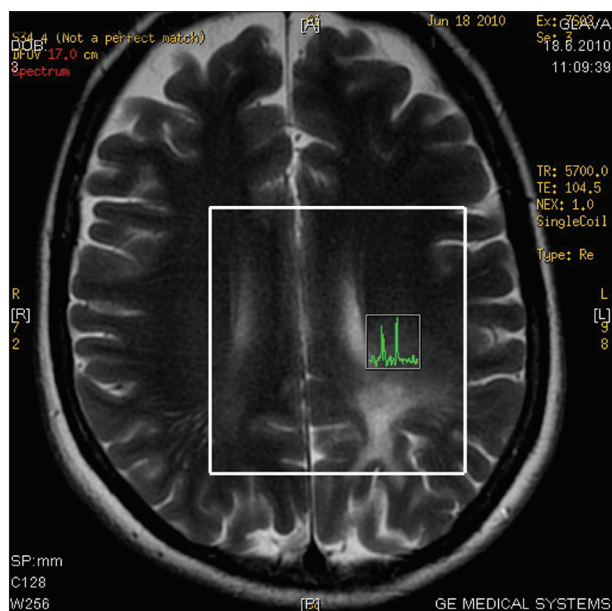


Figure 2. Magnetic resonance finding

changes. The orbits were without pathological changes. Nerve complexes VII to VIII were bilaterally of normal pathological form. The foramen magnum was free.

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

As concluded, the pathological process of the supratentorial white matter of the parietal segment according to MR characteristics corresponds to inflammatory/post-inflammatory sequels. Given the focal perilesional atrophy and suspicion of Rasmussen's encephalitis, an immunological examination of the cerebrospinal fluid was indicated in order to determine the presence of oligoclonal bands. However, the patient refused lumbar puncture. Due to the described change close to the speech center, cerebral biopsy was not undertaken. The decision of the Neurosurgical Consilium was that at the time there were no indications for surgical intervention. The patient was released with antiepileptic and antidepressant therapy. Follow-up MRI was performed at six months, one year, and five years after the dismissal. Even after five years, MRI and spectroscopic findings are unchanged, while the clinical condition of the patient remains stable and unchanged. There is, however, the following dilemma: Is this adult-onset Rasmussen's encephalitis?

DISCUSSION

In about 10% of cases, RE onset occurs after the 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, for example, mild contralateral atrophy [8, 9].

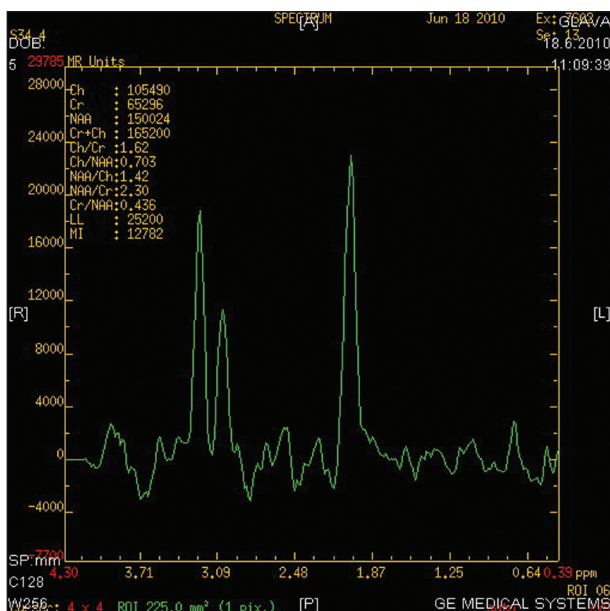


Figure 3. Spectroscopy finding

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, and (c) a primary autoimmune process. The first two hypotheses have been confirmed by case reports of patients with minor infections before the disease onset (our patient was subfebrile) [9]. Recently, three phases of the disease have been described: the prodromal phase, lasting 0–8.1 years, the acute phase, with manifested symptoms of the disease (seizures, neurological disorders: hemiparesis, hemianopia, disorders of cognitive functions, and speech disorders) of the average duration of 8 months, as in our patient, and the third, residual phase, with the stabilization of the condition, with variable duration [10].

Based on the suggested diagnostic criteria for RE [8], presented in Table 1, our patient has fulfilled two of the 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 T2 FLAIR hyperintense 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 is scientific evidence that electrocardiography can contribute to reaching the diagnosis of RE in the early phase of the disease [9].

Serial MRI findings of several patients have been published in recent years. The opinion of Chiapparini et al. [11] is that MRI demonstrates the progression of RE and can suggest diagnosing the disease in the early phase, often before the onset of neurological deficits. PET and SPECT are usually used in the late phase and do not provide con-

crete results. Early RE diagnosis is crucial in the selection of patients who require aggressive medicamentous therapy or surgical intervention such as hemispherectomy.

According to Rasmussen [12] and Rasmussen and Andermann [13], standard cerebrospinal fluid tests are not reliable for the confirmation or rejection of the RE diagnosis. Serological cerebrospinal fluid tests are usually applied in order to exclude infections by well-known neurotropic viruses. Our patient refused lumbar puncture. In most cases, the PET method detects large hypometabolic zones of the involved hemisphere, while new zones with focal hypermetabolism are found in a somewhat lower number [11, 14]. Lee et al. [15] have proposed that PET may guide brain biopsy in cases with inconclusive or normal MRI findings, especially in the early stages. sMRI investigation indicates that lowering the level of N-acetylaspartate (NAA) and increasing (or normal) levels of 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, SPECT, and sMRI 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 could be sufficient in making the diagnosis (Table 1).

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

diagnosis are necessary. In our patient, differential-diagnostic considerations were aimed at the following: 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 can show whether there is 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 the speech center, it was not performed in our patient.

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

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 adults can be a challenging diagnosis.

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Дијагностичке дилеме код Расмусеновог енцефалитиса одраслих

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САЖЕТАК

Увод Расмусенов енцефалитис (РЕ) ретко је, прогресивно, инфламаторно обољење мозга које је тешко доказати код 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 је показао следеће: окципитопаријетално лево у дубокој белој можданој маси, као и субкортикално уочава се T2/flair хиперинтезна промена, T1 хипоинтензна промена захвата *corpus callosum*.

Спектроскопски се евидентира повишена вредност односа холин / креатинин (Кр) (2,12), редукован ниво азот-ацетил-аспартата / Кр (1,27), повећана вредност миоинозитола / 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 и указује на то да ову дијагнозу треба узети у обзир код болесника било којег узраста са одговарајућом клиничком сликом.

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