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Symptomatic Epilepsy in Inflammatory Demyelinating Diseases

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Published data and our own observations are used to present the features of symptomatic epilepsy in multiple sclerosis, post-infectious acute disseminated encephalomyelitis, isolated cerebral angiitis, and Rasmussen's encephalitis. Examples of the clinical analysis of the diagnostically most complex cases of inflammatory and demyelinating diseases with epilepsy syndrome are presented. The MRI features of structural brain injuries are discussed. The role of additional laboratory investigations, including cerebrospinal fluid analysis, in the diagnosis of this pathology, is discussed.

Keywords: symptomatic epilepsy, multiple sclerosis, acute disseminated encephalomyelitis, idiopathic cerebral angiitis, Rasmussen's encephalitis.

Many cases of epilepsy are known to result from structural damage to the brain and are regarded as secondary, or symptomatic cases. Single and particularly repeated seizures are therefore direct indications for MRI scans. When MRI scans show multifocal lesions to brain tissue, the possibility of an inflammatory demyelinating process, particularly multiple sclerosis (MS), must be considered.

Cases in which epilepsy develops on the background of MS are the most common and have been addressed in a multitude of Russian and foreign publications, including contemporary reviews [1, 3, 8, 11]. The main scientific aspects of epilepsy in MS are the correlation between clinical signs with MRI changes and prognostic factors and the course of epilepsy on the background of immunotropic and antiepileptic treatment. Diagnostic difficulties arise in situations in which epilepsy is the first manifestation of MS [3]. In cases in which the clinical-radiological and laboratory data do not indicate MS but point to active inflammation or demyelination, nosological diagnosis can be extremely complex. Diseases in this category include variants of acute disseminated encephalomyelitis (ADEM), types of isolated cerebral angiitis (idiopathic and post-infectious), inflammatory encephalopathies (idiopathic and paraneoplastic limbic encephalitis), epileptic encephalopathies (Rasmussen's encephalitis), and rare cases of systemic inflammatory diseases.

The aim of the present work was to summarize our own observations of the features of symptomatic epilepsy in MS and clinical analysis of the diagnostically most complex cases of inflammatory and demyelinating diseases in which the leading clinical syndrome is epilepsy.

MATERIALS AND METHODS

Case details and their positions in the overall structure of these diseases are shown in Table 1.

The most frequent cases of symptomatic epilepsy were seen in patients with MS, though the incidence of epilepsy in MS was significantly lower than in disseminated encephalo-

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TABLE 1. Details of Cases of Demyelinating and Inflammatory Diseases with Symptomatic Epilepsy

Disease	Number of cases with epilepsy	Age of patients at disease onset in cases with epilepsy, years	Duration of disease at onset of epilepsy
Multiple sclerosis	10 out of 1240 (0.8%)	14–36 (mean – 23)	1–7 years (mean 3.0 years)
Acute disseminated encephalomyelitis	2 out of 51 (3.9%)	23 and 30	Epilepsy was the initial symptom
Isolated cerebral angiitis	2 out of 18 (11.1%)	18 and 22	One year in 1 case; onset with epilepsy in the other
Other inflammatory diseases	1 out of 6	14	Epilepsy was the initial symptom

Note. The "other inflammatory diseases" were Rasmussen's encephalitis (n = 1), neurosarcoidosis (n = 2), neurolupus (n = 2), and Behçet's disease (n = 1).

myelitis and vasculitis. None of our cases showed epilepsy as the debut of MS and it was not dominant as a more isolated syndrome. In contrast, four out of five cases of other neurological diseases had repeated epileptiform seizures as the initial symptom and in three cases these subsequently formed the "core" of the clinical picture. The characteristics of each of these diseases, relevant published data, clinical examples, and evaluations are presented in more detail below.

RESULTS AND DISCUSSION

Multiple sclerosis. The incidence of epilepsy in MS ranges from 0.5% to 8.3%. Meta-analysis of the largest studies shows that the incidence in population cohorts is 2.9% (95% confidence interval (CI): 2.3–3.7%), compared with 2.1% (95% CI: 1.9–2.3%) in patient cohorts [11]. Considering the incidence of MS and the incidence of epilepsy in the general population, the probability that these will be combined (comorbid) as two independent diseases (MS and epilepsy) in one patient is very low: $epilepsy \cap \cap PC = 6/10^3 \cap 1/10^3 = 6/10^6$, i.e., six cases per million people.

Data from the St. Petersburg and Leningradskaya Oblast MS Patients Register (patients receiving immunomodulatory treatment) indicate that symptomatic epilepsy occurred in 10 of 1240 cases, which is 0.8%. This is lower than in a number of cited reports. It should be noted that the group of patients with symptomatic epilepsy in MS did not include patients with single epileptic seizures in their histories, with unclear paroxysmal disorders, or patients in whom diagnoses of epilepsy (including symptomatic epilepsy with known causes) were established long before the onset of MS, i.e., cases of probable comorbidity. Details of our observations are shown in Table 2.

The study patients with MS and epilepsy included six women and four men. As noted above, unlike some other authors [3], we did not see epileptic seizures at the debut of MS. However, epilepsy formed early: 80% of patients had epilepsy in the first 1–3 years of illness. This corresponds to the stage of marked inflammatory activity of MS. The link of epilepsy with inflammation in MS is indicated by various other data. Thus, frequent occurrence of repeated epileptic seizures were noted during clinical exacerbations of MS, as was the possibility that they could disappear spontaneously after settling of exacerbations or treatment with corticosteroids [11]. In two patients, seizures stopped during the first year after initiation of immunomodulatory treatment of MS, and in one case frequent daytime simple focal seizures regressed after corticosteroid treatment of MS exacerbations. Two patients showed inflammatory activity on MRI scans (foci accumulating contrast agent) in investigations performed during the early period of seizures.

Use of improved MRI methods in recent years has provided support for the role of inflammation in the cerebral cortex in the formation of epilepsy in MS. Thus, MS patients with epilepsy had focal cortical lesion volumes five times greater than that in MS patients without epilepsy [8]. Using standard methods (T2SE), a number of cases also showed foci in the cortex, though use of double inversion recovery impulse sequences with suppression of white matter and cerebrospinal fluid (CSF) signals (DIR-GM) not only provided better visualization of foci, but also more precise determination of their locations, with identification of juxtacortical, corticosubcortical, and intracortical lesions (Fig. 1).

The frequencies of different types of seizures in MS, on the basis of data from large studies, are as follows: simple focal seizures occur in 21% of cases, complex focal seizures in 11%, secondary generalized seizures in 34%, and primary generalized seizures in 34% [11]. The signs of epilepsy in this group of patients were more severe as compared with published data. Secondary generalized seizures were seen in nine out of 10 patients, in six of whom seizures were polymorphic: both generalized seizures and simple and complex focal seizures were seen. Three out of 10 patients showed severe courses of epilepsy, with serial seizures and status epilepticus. In one female patient, status epilepticus of secondary generalized seizures requiring prolonged treatment in the intensive care unit was the first manifestation of symptomatic epilepsy, which developed five years after the onset of MS. Repeated status epilepticus (without single seizures) developed in one female patient at one year of continuous carbamazepine treatment. Neither

TABLE 2. Features of Symptomatic Epilepsy in MS

Case No.	Duration of MS before epilepsy, years	Type of seizure	Effective treatment	Treatment of MS (at the onset of epilepsy)
1	3	Simple focal, secondary generalized	Carbamazepine + lamotrigine	Glatiramer acetate
2	5	Secondary generalized (status epilepticus)	Valproates + lamotrigine	Interferon-β-1a (44 μg)
3	2	Complex focal, secondary generalized	Carbamazepine	–
4	2	Secondary generalized	Carbamazepine	Interferon-β-1a (44 μg)
5	1	Secondary generalized	Carbamazepine	–
6	1	Complex focal, secondary generalized	Carbamazepine	–
7	3	Simple focal, secondary generalized (status epilepticus)	Phenytoin	Interferon-β-1a (44 μg)
8	7	Simple focal	No treatment, regression after recovery from exacerbation	–
9	3	Complex focal, secondary generalized (serial)	Regression after initiation of treatment for MS (interferon β-1b)	–
10	3	Secondary generalized with subsequent addition of simple focal	Regression after initiation of treatment for MS (interferon β-1b)	–

Note. An effective treatment is taken as a treatment with agents (antiepileptics or agents for the treatment of MS) leading to complete cessation or significant decreases in the frequency of epileptic seizures.

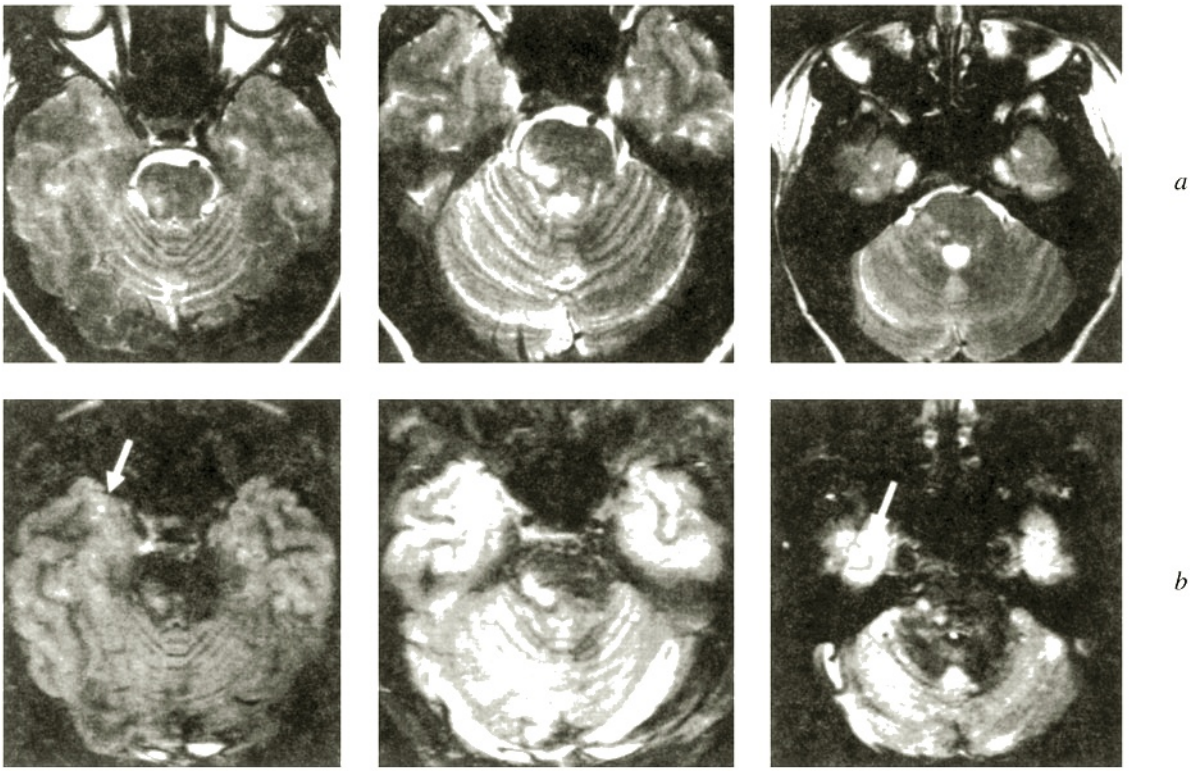

Fig. 1. Brain MRI scan in multiple sclerosis with symptomatic epilepsy. Sequence of images in the axial projection: *a*) T2SE shows multiple foci in the pons (mainly on the right) and right temporal lobe; *b*) DIR-GM impulse sequence provides better visualization of foci in the right temporal lobe (arrows) and classifies them as intracortical.

episode was accompanied by clinical signs of MS exacerbation, though treatment of one required corticosteroids. Over the next five years, there were no seizures, on the background of treatment with valproates and lamotrigine. The characteristics of this case of MS were the early onset of demyelinating disease (at age 14 years), a high frequency of exacerbations (3–4 per year in the first three years of disease, until treatment started), and a large focal lesion volume on MRI scans. In most cases, effective antiepileptic treatment consisted of carbamazepine at standard doses; treatment in two patients included two antiepileptic agents (AEA). These results are consistent with the type of epileptic seizures and their corresponding standard treatments, as well as with published data. In three cases, seizures regressed without AEA: in one patient after treatment of the exacerbation and in two after initiation of immunomodulatory treatment with interferon-β-1b. By the time of onset of epilepsy, three of six patients were receiving immunomodulatory treatment for MS (Table 2). Two cases with poorly controlled epilepsy required repeated withdrawal of agents for the treatment of MS (interferon-β-1a) in accordance with the instructions for use.

In summary, our data on the symptomatology of epilepsy in MS indicate that the need for diagnostic investigations after the first paroxysmal event should be emphasized. EEG investigations and brain MRI scans are essential. On formation of epilepsy, i.e., when repeated seizures develop despite possibille regression on the background of the anti-inflammatory treatment of MS, AEA are required in accordance with the nature of the seizures. In cases of the onset of seizures on the background of symptoms of MS exacerbation, treatment starts with courses of parenteral corticosteroids.

Acute disseminated encephalomyelitis. More than half of cases of ADEM in adults develop an average of 1–3 weeks after infection, usually respiratory [20]. According to the international diagnostic criteria [12], ADEM is characterized by the subacute development of multifocal neurological symptoms, along with encephalopathy, apparent as disorders of consciousness or behavior. Encephalopathy is an obligatory sign for confident diagnosis. When the condition is monophasic, there are fluctuations, with regression and the appearance of new symptoms over periods of three months. Brain MRI scans demonstrate different sized and often large (more than 1–2 cm in diameter) foci of hyperintense signal (in the T2SE and FLAIR regimes), mainly in the white matter of the brain but not infrequently with involvement of the gray matter. Depending on the severity of the pathological processes, foci may be hypointense in the T1SE regime, subsequently transforming into cystic-gliotic zones, or may disappear in milder cases. The CSF not infrequently shows lymphocytic pleocytosis or elevated protein levels. There are no specific biological markers for ADEM.

Epileptic seizures in ADEM are seen more frequently in children (8–34%) and are significantly rarer in adults (3–4%) [14–16, 21]. Our series of cases included 51 adult patients with ADEM, of whom two (3.9%) had repeated generalized epileptic seizures [4]. The case described below reflects the dominant nature of epileptic syndrome in the clinical picture and the complexity of the differential diagnosis.

Patient S was born in 1979. She experienced mild symptoms of catarrh from December 15, 2009, with headache and a subfebrile temperature. On this background, she developed a series of generalized tonic-clonic seizures on December 21, 2009. The patient was hospitalized as an emergency and admitted to the department of neurology of a general hospital. On examination: the patient had malaise and nystagmus on looking to the right. CSF December 22, 2009: cytosis $23 \cdot 10^6$/liter (predominantly mononuclear cells), protein 0.52 g/liter, glucose 5.48 mM. Treatment was with antibiotics, corticosteroids (i.v. followed by p.o. dexamethasone). Seizures did not recur.

On December 30, 2009, the patient was transferred to an infection hospital with suspected viral meningoencephalitis. Neurological status: malaise, impaired short-term memory, horizontal nystagmus on looking to the right, mild bilateral dynamic ataxia. CSF December 30, 2009: cytosis $10 \cdot 10^6$/liter, mononuclear cells, PCR for herpesviruses (HSV1, HSV2, CMV, EBV, VZV, HHV6) negative, oligoclonal IgG bands absent. Serum antibody titers to herpesviruses insignificant. Brain MRI scan (1.5 T) December 31, 2009: FLAIR images showed minor changes in the MRI signal from the cortex of the mediobasal areas of the temporal lobes and a hyperintense focus of 5 mm in the projection of the left hippocampus (Fig. 2, *a*). Treatment with parenteral aciclovir (for three weeks) was started on December 31, 2009 and with AEA (Depakin Chrono with dose titration) on January 5, 2010, and there were no seizures. A brain MRI scan (1.5 T) on January 10, 2010 showed improvement, with regression of signal changes in the right temporal lobe. The 5-mm focus in the projection of the left hippocampus persisted; images in the DWI regime showed a zone of hyperintense signal from the cortex of the left temporal lobe and adjacent leptomeningeal space. There were no destructive changes or volume effects on surrounding structures. Seizures recurred on January 11, 2010 on the background of decreases in the dexamethasone dose – these were secondary generalized seizures at a frequency of 1–2 per day. A further parenteral course of dexamethasone followed by oral dexamethasone was given, along with three plasmaphereses. From January 20, 2010, on the background of repeated seizures, the patient developed stupor, profound right-sided hemiparesis, dysarthria, dysphagia, and increasing polyuria to 22 liters per day with hyponatremia. Methylprednisolone pulse therapy was started, followed by oral methylprednisolone, along with antidiuretic hormone and correction of antiepileptic treatment. A brain MRI scan (1.5 T) on January 24, 2010 showed new changes, more consistent with the pattern of ADEM. Discrete and fused foci of hyperintense signal on T2SE, FLAIR, and DWI

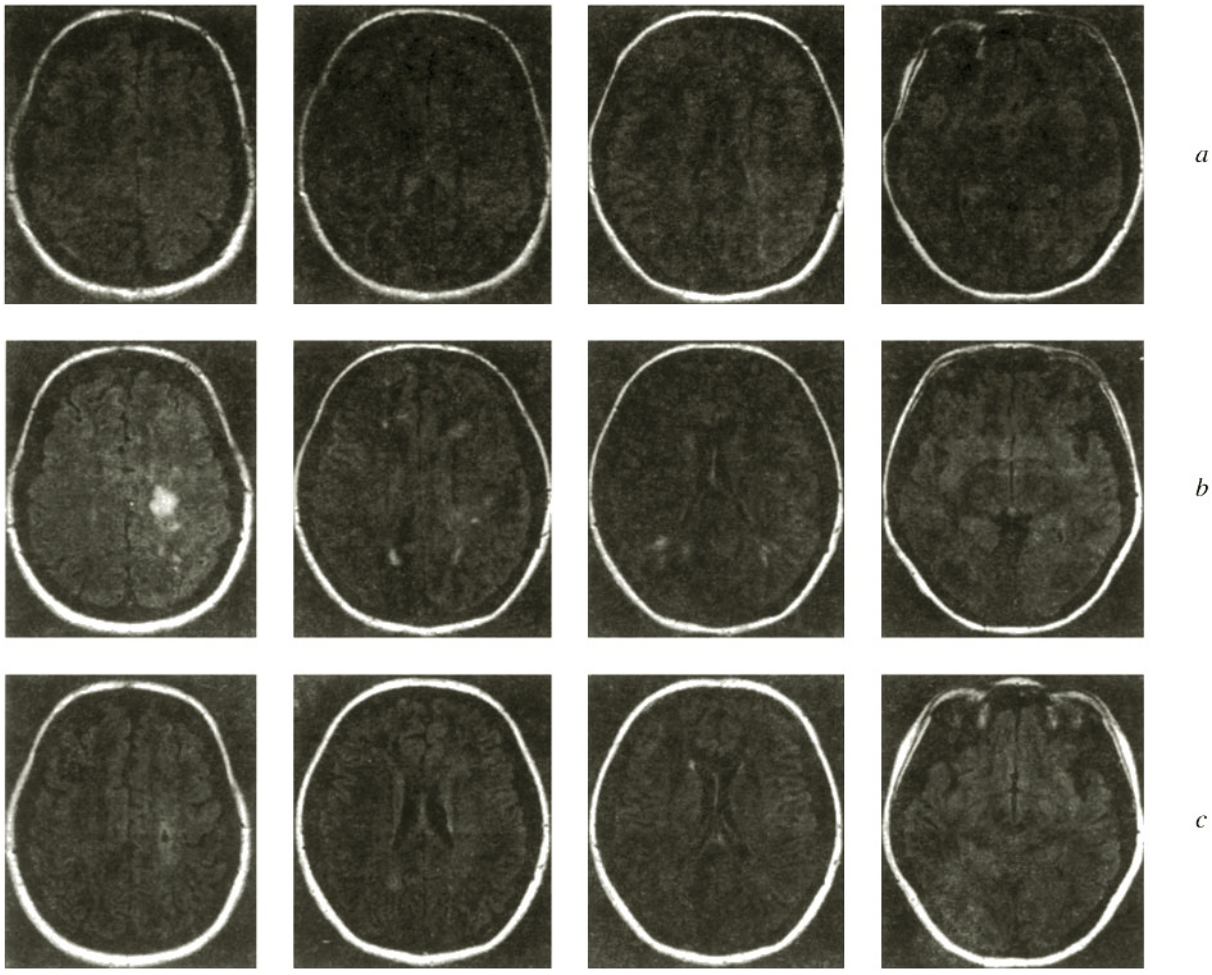

Fig. 2. Brain MRI scans, patient S, with diagnosis of "postinfectious acute disseminated encephalomyelitis." Sequence of images in the axial projection in the FLAIR regime: *a*) December 31, 2009 – minor increase in signal and smoothing of the gyri of the cortex of the insula of the left temporal lobe; *b*) January 24, 2010 – foci of hyperintense signal in the white matter of the frontal and parietal lobes, right temporal-occipital area; *c*) April 22, 2010 – regression of most foci, cystic-gliotic transformation of foci in the white matter of the left frontal lobe at the supraventricular level.

images, with sizes of up to 23 × 14 mm, were seen in the white matter of the frontal, parietal, and right temporal lobes of the brain in the periventricular regions and supraventricularly (see Fig. 2, *b*). MR angiography showed that the vertebral and basilar artery diameters were small (1.5 and 2 mm, respectively) and demonstrated decreases in peripheral blood flow. CSF February 8, 2010: cytosis $3 \cdot 10^6$/liter, mononuclear cells, protein 0.33 g/liter, PCR for herpesviruses negative. Oligoclonal IgG bands (in parallel serum and CSF samples) were absent, CSF myelin basic protein 2.2 ng/ml (normal <1 ng/ml). Serum antibody to onconeurological antigens (anti-Hu, Ri) absent.

On February 27, 2010, the patient was transferred to the neurology department. Neurological status: drowsiness, moderate impairment to short-term memory, focal temporal seizures 2–4 per day, sometimes with secondary generalization. Moderate right-sided hemiparesis, mild dysarthria; polyuria, and Cushingoid facies. At this time, the corticosteroid dose was reduced and polyuria was corrected (antidiuretic hormone), as was antiepileptic treatment (valproates, levotiracetam). A brain MRI scan (1.5 T) on March 2, 2010 showed improvements (on the background of corticosteroid treatment). Neurological status was characterized by complete regression of dysarthria, pyramidal and coordinatory impairments and improvement in cognitive functions. Focal temporal paroxysms persisted, developing at a frequency of 1–2 per day. Repeat CSF studies with general, virological, and immunological analysis showed no abnormalities except an increase in the myelin basic protein level. A brain MRI scan (1.5 T) on April 22, 2010 showed significant improvement, with decreases in the sizes of many of the foci, to the level of disappearance; the projections of several foci in the white matter showed cystic-gliotic changes (see Fig. 2, *c*).

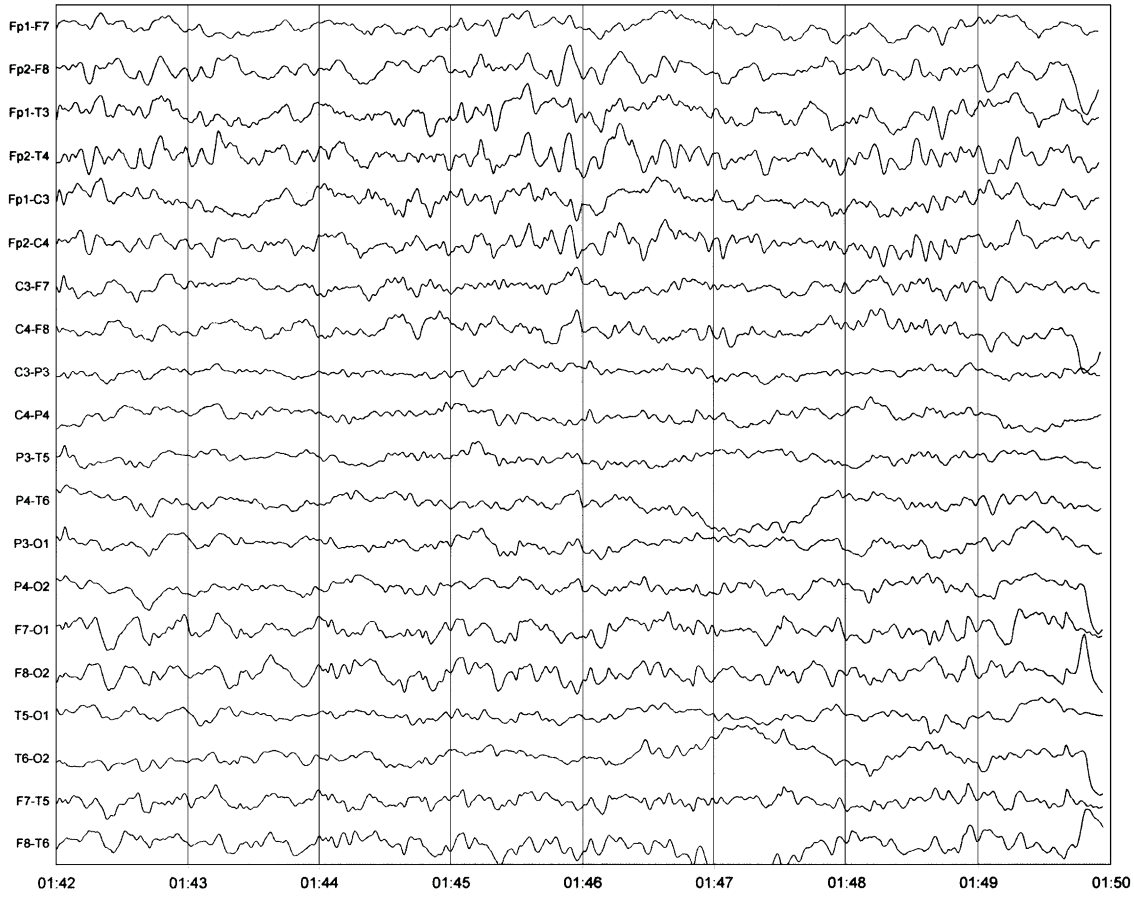

Fig. 3. EEG trace, patient S, May 31, 2010: epileptiform activity in the frontal and anterior temporal areas, more marked on the right.

Clinical signs over the next two months were characterized by stable focal temporal paroxysms with a frequency of one per day. An EEG recording on May 31, 2010 showed epileptiform activity in the frontal and anterior temporal areas, mainly on the right (Fig. 3). Focal changes in the left hippocampus seen on the MRI scan did not correspond to the EEG picture and were probably not the direct or sole cause of epileptiform syndrome.

Clinical diagnosis. Nosological group: acute disseminated encephalomyelitis; nosological form (variant): post-infection encephalitis (G04.8), symptomatic epilepsy.

It is apparent from these observations that neurological symptoms in this patient developed one week after the onset of an acute respiratory illness on the background of decreasing general signs of infection. Most known viruses of the respiratory group are not neurotropic and do not infect the nervous system. The role of respiratory infection in cases of this type is that they act as a trigger factor for a subsequent organ-specific inflammatory (autoimmune or infectious) process. The inflammatory nature of the process is supported by pleocytosis in the CSF.

Damage to the nervous system in this patient developed on the background of a subfebrile state: there was initially a series of generalized convulsive seizures with depression of consciousness (stupor) during the interictal period and subsequent memory impairment. These symptoms are most characteristic of herpes encephalitis, though repeat CSF investigations for herpes simplex viruses (HSV1, HSV2) and other herpesviruses did not identify any etiological role. It should be emphasized that the diagnostic sensitivity and specificity of the polymerase chain reactions (PCR) used here for CSF studies in herpes encephalitis are 95–100% from the second day of illness to the end of the first week of antiviral treatment, results being consistent with neuroimaging and brain biopsy data [13]. The patient also showed no increases in serum herpesvirus antibody titers. Brain MRI scans did not show the destructive changes in the temporal-frontal areas typical of herpes encephalitis, though changes in MRI signals in the temporal lobes, with subsequent rapid improvement, supported the occurrence of damage at the time of disease onset. Treatment with aciclovir prescribed on the basis of clinical

data and vital parameters suggestive of herpes encephalitis could undoubtedly have played a positive role in stabilizing the process had activation of herpes simplex virus occurred.

Significantly rarer than herpes encephalitis is limbic encephalitis (idiopathic or paraneoplastic), due to autoantibodies to neuronal or onconeuronal antigens (also expressed by various tumors). Epileptic seizures, disturbed consciousness, and memory impairments are the main clinical signs of limbic encephalitis. The disease damages the gray matter of the temporal lobes of the brain and MRI scans can visualize changes in the signal from the temporal lobes, including the hippocampus; nonspecific changes may be present or absent. The CSF shows pleocytosis and elevated protein, though there may be no change. The diagnosis may be supported by the presence of the corresponding autoantibodies in the serum: anti-Hu (association with small cell lung tumors), Ta/Ma2 (testicular tumors), or CRM5/CV2 (small cell lung tumors, thymomas), though this was not so in the present case. Variants of limbic encephalitis have recently been described due to autoantibodies to NMDAR and VGKC. Anti-NMDAR encephalitis is often encountered in young women (idiopathic or associated with ovarian teratoma), while encephalitis due to antibodies to VGKC is accompanied by hyponatremia and can be monophasic or can show spontaneous remission. Testing for the corresponding antibodies in our patient was not performed, so the suggestion that she had limbic encephalitis could not be confirmed. Anti-inflammatory and immunosuppressive treatment (corticosteroids and plasmapheresis) can promote both stabilization of status and improvements on MRI scans.

New diagnostic questions appeared in weeks 2 and 5, when epileptic seizures restarted on the background of antiviral treatment and decreases in corticosteroid doses, becoming polymorphic and then being accompanied by multifocal symptoms of loss of neurological functions. This did not correspond to the expected dynamic for herpes encephalitis or the signs of limbic encephalitis. MRI scans demonstrated new structural changes. Unlike the previously identified changes, these were located in the white matter of the brain. At this stage of illness, consideration of both the initial and subsequent clinical features, MRI scan data, and laboratory results indicated that the nature of the pathological process was entirely consistent with the international criteria for a diagnosis of ADEM [12, 19]. There was a greater than two-fold increase in the myelin basic protein concentration in the CSF, indicating active demyelination and confirming the demyelinating nature of the process. Multifocal demyelination of the white matter could not result from herpes or limbic encephalitis, neither of which was supported by laboratory investigations, though the possibility of these processes at the initial stage of the patient's illness could not be excluded completely.

Idiopathic angiitis of the central nervous system (IACNS). According to the ICD-10, IACNS is an inflammatory lesion affecting brain (and rarely spinal cord) vessels of unknown etiology. There are several synonyms in the scientific literature – primary CNS angiitis, isolated CNS angiitis, as well as benign variant angiitis [7]. The diagnosis in most cases is based on clinical characteristics and MRI scan data. These and other results are often nonspecific, so the diagnosis of isolated cerebral angiitis is difficult. MR angiography also fails to visualize changes in the walls of the small vessels most often involved in IACNS. The sensitivity of digital x-ray angiography in detecting changes interpreted as vasculitis, i.e., segmental constriction in multiple vessels, is less than 30% [17]. The informativeness of biopsies in investigating leptomeningeal vessels – the only method for diagnostic confirmation during life – is less than 50%, and in most cases the benefit:risk ratio does not justify this invasive intervention. No biological markers for IACNS are known, while CSF studies, sometimes revealing pleocytosis, confirm only the inflammatory nature of the process. Thus, the diagnosis of IACNS is in many cases a "diagnosis of exclusion."

IACNS is most often seen in women, and for the benign variant the female:male ratio is 4:1. In the most typical cases, the disease manifests as headaches (sometimes intense), epileptiform seizures, and stroke-like episodes of neurological dysfunction due to ischemia. The course of benign angiitis is not infrequently monophasic, though recurrences are sometimes seen. In severe forms, there is a stepwise progression of neurological deficit, with subsequent formation of typical "vascular" syndromes. Brain MRI scans in severe angiitis, demonstrating typical ischemic foci, allow the correct diagnosis to be established. In the benign variant, MRI scans, conversely, can provide an additional source of diagnostic errors, imitating demyelinating, infectious, or other processes. The case described below provides an example of the difficulties with the differentiation diagnosis.

Patient K, female, was born in 1984. She fell ill in December 2006 and was observed from the second month of illness.

The first episode of neurological dysfunction developed on December 5, 2006, with "disconnected" speech and dysphagia lasting a few minutes. On December 31, 2006 an episode lasted more than an hour, with moderate non-systemic vertigo and failure to understand conversational speech; she was unable to express thoughts and had agraphia. Such daytime episodes occurred over the next two months on the background of normal consciousness; episodes lasted 20–40 min and the main manifestations were vertigo and sensorimotor dysphasia, and sometimes paresthesia in the right side of the face. The absence of impairment to consciousness and a convulsive component, symptoms of functional loss, and the duration and incomplete stereotypy of the episodes provided evidence of their epileptiform nature. On January 17, 2007 the EEG showed no pathological changes. A brain MRI scan on January 18, 2007 showed multifocal lesions mainly of the white (with

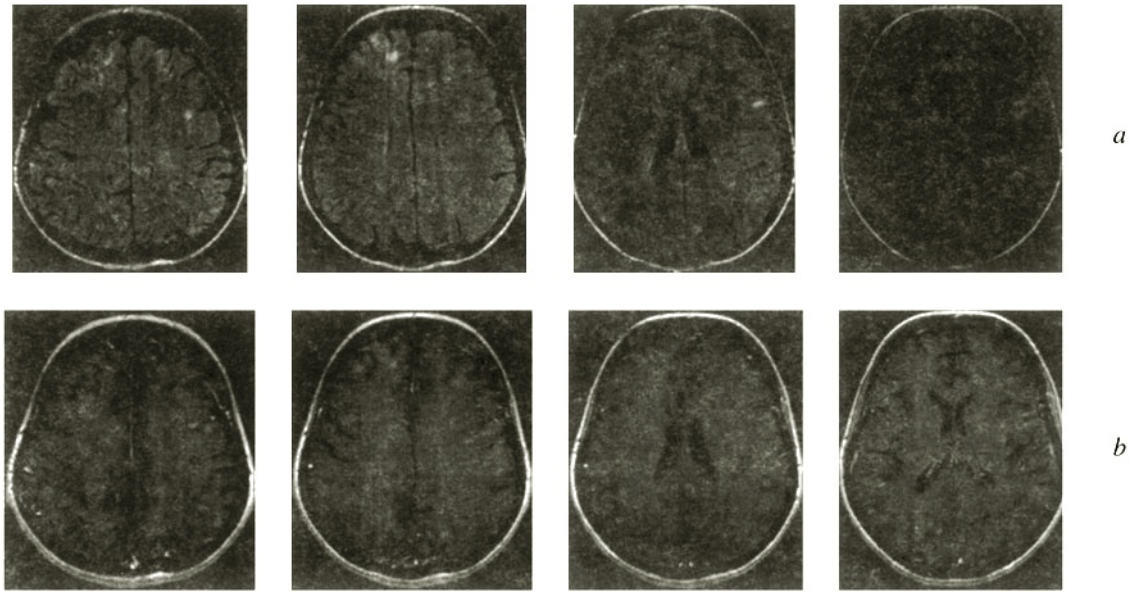

Fig. 4. Isolated cerebral angiitis. Brain MRI scan, patient K. Sequences of images in the axial projection at the supraventricular and ventricular levels: *a*) bilateral foci of hyperintense signal in the subcortical and deep zones of the white matter (FLAIR impulse sequence); *b*) most foci accumulate contrast agent (post-contrast T1-weighted images).

involvement of the gray) matter located in the frontal lobe and temporal cortex, and with a zone of altered signal in the periventricular area of the posterior horn of the right lateral ventricle. Focus size ranged from 3 to 6 mm and the outlines were poorly defined; intravenous contrasting was not performed. MR angiography revealed a closed circle of Willis and the absence of stenoses and vascular anomalies. Neurological status on January 19, 2007: no focal or conduction symptoms.

CSF investigation on January 24, 2007: cytosis $18 \cdot 10^6$/liter, mononuclear cells, protein 0.33 g/liter, PCR for herpesviruses (HSV1, HSV2, CMV, EBV, VZV, HHV6), hepatitis C virus, parvovirus B19, and *Borrelia* negative, PCR for *Chlamydia trachomatis* positive, oligoclonal IgG bands (in parallel serum and CSF samples) absent, free Ig light chain levels normal. There were no inflammatory changes in the blood and serological studies showed no potentially neurotropic infections such as measles, rubella, syphilis, or HIV. Systemic and organ-specific lesions were also not detected.

Considering the MRI changes and CSF pleocytosis, it was suggested that the patient had a subacute multifocal encephalitis and a parenteral interferon inducer (Neovir) was given along with mild antiepileptic treatment (Pantogam).

A brain MRI scan (1.5 T) on February 10, 2007 with intravenous contrasting on the background of immunomodulatory treatment showed improvement, with partial regression of foci. No contrast accumulation zone was seen. The patient continued treatment for two months, during which episodes were not repeated. After independent withdrawal of treatment on April 12, 2007, repeat daytime episodes of vertigo and sensorimotor dysphasia lasting 2–7 min occurred at a frequency of 1–3 per month, one being followed by severe headache and nausea for 2.5 h. On September 2, 2007, the patient developed a secondary generalized clonic seizure followed by severe headache. An EEG on September 3, 2007 showed irregularity of the α rhythm with persistence of zonal differences in the baseline recording, with no pathological reactions on functional tests. No hemispheric foci of pathological activity were seen. A brain MRI scan (1.5 T) with intravenous contrasting on September 5, 2007 showed subcortical foci in the frontal, parietal, and right occipital lobes, zones of unaltered signal in the subcortical areas of the temporal lobes following the course of the gyri, and a single focus in the posterior part of the left hippocampus. No new foci of accumulation of contrast agent were seen.

At this stage, the picture consisted exclusively of epileptiform syndrome with signs of progression in the form of polymorphic seizures on the background of normal neurological status, the absence of pathological changes on the EEG, and the absence of active disease on the MRI scan. The patient received a course of antiviral treatment (Famvir) and an antiepileptic agent was selected (clonazepam). Over the next two years, occasional focal and secondary generalized (nocturnal) seizures occurred at a frequency of one every 3–4 months. An EEG recording on April 23, 2008 showed deterioration, with the appearance of stable regional epileptiform activity in the left temporal area and bilateral sharp wave discharges in baseline conditions. In relation to

a planned pregnancy, an elective brain MRI scan (1.5 T) with intravenous contrasting was performed on June 17, 2009, showing persistence of foci which were hyperintense in the T2SE and FLAIR regimes and isointense in the T1SE regime; these were of the previous size and locations, including the focus in the projection of the posterior basal parts of the left hippocampus. The cerebral ventricles were not dilated. Marked activity of the pathological process was seen as the accumulation of contrast agent by foci located subcortically in the frontal, temporal, and parietal lobes (Fig. 4). No new signs of clinical activity were seen at this time. Additional immunological serum investigations demonstrated autoantibodies to vascular epithelium (HUVEC). Overall, the data most likely evidenced active cerebral vasculitis. Medication was subsequently limited to minimal doses of AEA. The pregnancy progressed normally and ended with a term delivery of a healthy child.

Clinical diagnosis: isolated cerebral angiitis and symptomatic epilepsy with occasional focal and secondary generalized seizures.

This case is an example of an inflammatory neurological disease consisting exclusively of epileptiform syndrome and presenting significant difficulties in the nosological diagnosis. The diagnosis of isolated cerebral angiitis was based only on indirect indicators – because of the absence of direct indicators and the lack of known nosological forms providing a better explanation of the clinical and MRI features of the case.

The CSF pleocytosis during the initial symptoms and the MRI data at 2.5 years, which revealed impairments to the permeability of the blood-brain barrier at foci (accumulation of contrast agent), unambiguously point to an active inflammatory process. Inflammation, along with subcortical foci in both hemispheres, initially suggested neuroinfection or a demyelinating disease. The three-year history did not support these proposals. The clinical-radiological picture did not correspond to lesions typical of known infections, including herpes and opportunistic infections. In addition, it is difficult to explain the pathogenesis of a neuroinfection debuting as multifocal encephalitis and not producing new foci in subsequent years in the presence of inflammatory activity in the initial foci. Over three years of illness, the patient showed no clinical-radiological or laboratory evidence of MS [18], ADEM [12], or other known inflammatory demyelinating diseases, such that these diagnoses would be ungrounded. In this situation, the best supported diagnosis is isolated cerebral angiitis. The clinical picture of repeated "stroke-like" episodes probably resulting from ischemia is characteristic: the duration of the attacks, the symptoms of functional losses corresponding to the vascular basins, and headaches typical of vasospasm. It is known that lesions in IACNS can be selective, i.e., can involve vessels of a particular diameter and location, usually small arteries and arterioles, and sometimes veins and venules. As the causes of this heterogeneity have not been studied, no especially typical MRI pattern can be identified, such that radiological signs may show some similarity with those of a variety of multifocal processes [9]. MRI scans in angiitis mainly show perivascular changes in the parenchyma of the brain, which are also heterogeneous and consist of segmental zones of edema, chronic ischemia, and microscopic infarcts and hemorrhages, sometimes with reactive gliosis, demyelination, and axon death [17]. In our case, antibodies to vascular endothelium supported the presence of angiitis. The location of the process identified it as *isolated angiitis*. Whether they were primary (idiopathic) or secondary (infectious, virus-induced) cannot yet be determined. The positive PCR result for *Chlamydia trachomatis*, identifying the presence and replication of this organism in the CNS, means that a role for this pathogen as a trigger cannot be excluded. The same may apply in relation to various herpesviruses whose role in inducing vasculitis is known and for which the incidence of decreased latency in blood and nervous system cells in the population is 65–99%. "Subacute" inflammation in vessels in selective locations may result from the characteristics of the infection, and exacerbation depends on the cyclical nature of the reactivation of the infective or autoimmune process. Progression of epilepsy (the process of epileptogenesis) does not always coincide with the activity of the underlying disease, which can be seen in the case described here. Symptomatic epilepsy develops in the presence of particular lesions to the central nervous system (epileptogenic lesions), subsequently forming pacemaker and epileptogenic zones in the cortex which serve as independent sources of subsequent seizures [10].

Rasmussen's encephalitis. This rare inflammatory neurological disease, whose main manifestations are epilepsy (often refractory to medication) and atrophy of one of the cerebral hemispheres. According to current concepts, Rasmussen's encephalitis is an immunologically mediated disease whose pathogenesis involves both cellular mechanisms (T lymphocytes) and autoantibodies to components of nervous tissue. Suggested infective etiologies or infective triggers have not been found, though they have not been completely excluded.

In accordance with the international diagnostic criteria [5], confident diagnoses require three criteria of group A and, if these are not completely fulfilled, two criteria of group B. Group A: 1) focal attacks (with or without *epilepsia partialis continua*) and unilateral cortical deficit; 2) EEG showing unilateral slowing (with or without epileptiform activity) and unilateral onset of seizures; 3) MRI scans showing unilateral focal atrophy of the cortex, as well as a) hyperintense signal (T2SE, FLAIR) from the gray or white matter, or b) hyperintense signal or atrophy of the head of the ipsilateral caudate nucleus. Group B: 1) *epilepsia partialis continua* and progressive unilateral cortical deficit; 2) MRI scans showing progressive unilateral focal cortical atrophy; 3) biopsy data showing predominantly T cell encephalitis, microglial activation, and reactive astrogliosis.

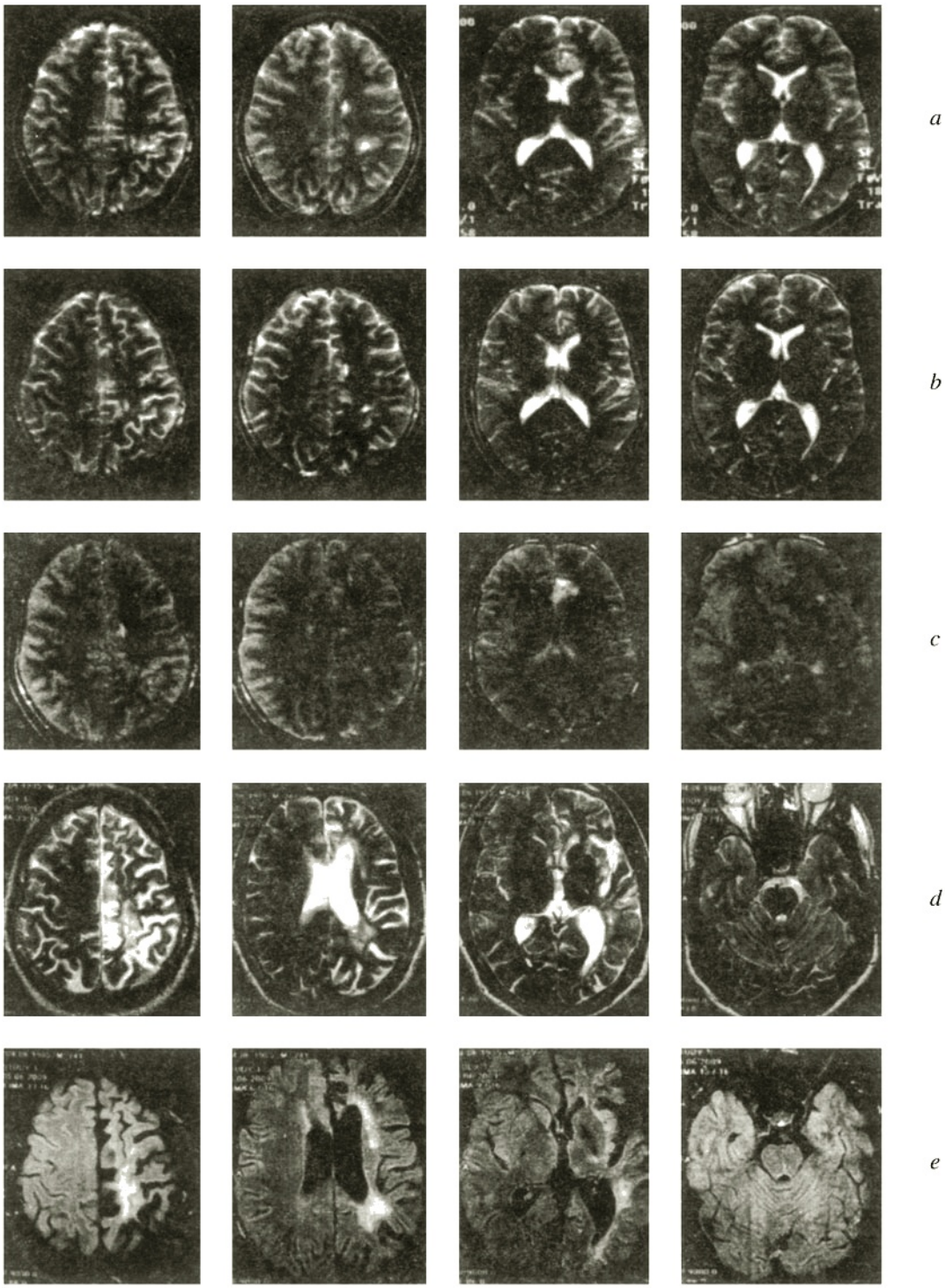

Fig. 5. Rasmussen's encephalitis. Sequences of images in the axial projection at the supraventricular and ventricular levels (*a*–*e*). *a*) February 21, 2000 – foci of hyperintense signal of irregular shape in the subcortical white matter of the frontal and parietal lobes of the left hemisphere, some with perifocal edema (T2-weighted regime); *b*) May 7, 2001 – regression of perifocal edema and decreases in sizes of foci at the supraventricular level, along with the largest subcortical focus in the mediobasal parts of the left frontal lobe (T2-weighted regime); *c*) June 6, 2002 – deterioration, with appearance of new foci (in the left frontal lobe at the supraventricular level and in the anterior parts of the left insula), increases in the sizes of foci in the mediobasal parts of the left frontal lobe, propagating to the adjacent cortex and genu of the corpus callosum (PD); *d*) June 5, 2009 – extensive diffuse focal changes in the white matter of the left hemisphere and cortex of the left insula, marked atrophy of the left hemisphere (T2-weighted regime); *e*) June 5, 2009 – similar findings, FLAIR regime.

The disease generally develops in children or adolescents and progresses in stages [2, 5]. In the prodromal stage, which averages seven months (but can be absent or can last up to eight years), there are occasional seizures and mild hemiparesis. The acute stage lasts an average of 4–8 months. This is characterized by frequent seizures (particularly simple focal and *epilepsia partialis continua*). Hemiparesis progresses and hemianopsia, cognitive impairments, and aphasia develop, affecting the dominant hemisphere. The residual stage then starts, during which frequent seizures and stable neurological deficit continue. Epilepsy is not infrequently severe and resistant to treatment, which is an indication for surgical treatment. Cases of Rasmussen's encephalitis without epilepsy have been described. The case described below provides evidence of the heterogeneity of the manifestations of this rare disease and the associated difficulties in the differential diagnosis against ADEM.

Patient G, male, was born in 1985 and fell ill in February 2000 at age 14 years.

Disease started with secondary generalized convulsive seizures, preceded by brief numbness in the right limbs. Repeated generalized seizures developed quickly and were followed by right-sided hemiplegia. The patient was admitted to the department of neurology and the following observations were recorded: general cerebral symptoms, frequent recovery of motor functions to the level of mild right-sided hemiparesis, repeated Jacksonian motor seizures with secondary generalization, and sensory Jacksonian seizures. A brain MRI scan on February 21, 2000 revealed multifocal lesions to the white matter: six foci of different sizes, of irregular shape, mainly subcortical, in the frontal and parietal lobes of the left hemisphere (Fig. 5). CSF investigations on March 6, 2000 and April 5, 2000 showed cytosis $(2–4)\cdot10^6$/liter, mainly mononuclear cells, protein 0.14 g/liter, and a free Ig kappa chain concentration of 0.075 μg/ml, which was 1.5 times higher than normal (active immune response). Investigation of the patient using visually evoked potentials and Doppler scans of the brachiocephalic vessels revealed no pathological changes. The EEG showed slowed activity, though there were no epileptic phenomena. Epidemiological and laboratory data which might provide evidence of an infective process were negative. Nonetheless, the patient was treated with antibiotics (i.m. ceftriaxone for two weeks), corticosteroids (i.m. prednisolone), and antiepileptics (Benzonal). The patient was discharged with the diagnosis: "leukoencephalitis with mild right-sided hemiparesis and epileptiform syndrome."

A brain MRI scan on May 23, 2000 showed no significant change, though FLAIR images visualized nine foci, including one focus in the right hemisphere (in the mediobasal parts of the right temporal lobe). MRI scans on November 3, 2000 and May 7, 2001 showed clear improvement, with decreases in the sizes of some foci (see Fig. 5, *b*). A brain MRI scan a year later, on June 6, 2002, showed deterioration, with enlargement of the focus in the mediobasal parts of the left frontal lobe, extending to the adjacent cortex; several new round cortical foci appeared, along with foci in the corpus callosum (see Fig. 5, *c*), evidencing renewal of disease activity and similarity to the picture seen in MS (albeit without paraventricular and infratentorial foci) or disseminated encephalomyelitis. Occasional focal motor seizures persisted, with right-sided pyramidal failure.

Considering the deterioration seen on the MRI scan, the patient was readmitted for investigation. An EEG recording on October 1, 2002 showed sharp waves in the left parietal and right temporal areas after hyperventilation, resulting in prescription of carbamazepine. The patient was discharged with a diagnosis of recurrent disseminated encephalomyelitis.

From age 17 years, the patient was reviewed at the Epilepsy Center with a diagnosis of sequelae of leukoencephalitis and symptomatic epilepsy. Treatment was with lamotrigine from 2006. In 2007, there was an increase in the frequency of focal and generalized seizures, with a tendency to serial seizures, along with the onset of dysarthria. A brain MRI scan on June 5, 2009 showed marked progression of diffuse focal changes in the white matter of the left hemisphere, again suggesting the development of a demyelinating disease, along with marked left-sided hemiatrophy of the brain (see Fig. 5, *d*, *e*).

The patient was investigated in the neurology clinic in 2010 following repeated serial secondary generalized seizures: neurological status included moderate cognitive and memory disorders, fluctuating motor dysphasia, loss of deep reflexes, more so on the right side, and right-sided hemihypesthesia with complete loss of proprioception in the right lower limb. Mild bilateral dynamic and static-locomotor ataxia was present. An EEG trace on June 18, 2010 showed clear diffuse changes in brain bioelectrical activity evidencing a marked reduction in the functional activity of neurons in the cortex of the left hemisphere. Regional slowing of baseline activity in the left frontal, temporal, and parietal areas persisted. There was spontaneous moderate regional epileptiform activity consisting of single sharp waves in the left frontal area (Fig. 6). Duplex scanning of the major vessels of the head and neck on June 17, 2010 revealed no pathological changes. CSF studies on June 17, 2010 showed that the cellular composition and protein levels were within the normal ranges and there were no oligoclonal IgG bands. Antiepileptic medication was reviewed (Convulex, topiramate) and no generalized convulsions occurred over the next month.

Clinical diagnosis. Rasmussen's encephalitis and symptomatic epilepsy with frequent complex focal and secondary generalized tonic-clonic seizures.

This case presented significant difficulties in the differential diagnosis. The diagnosis of Rasmussen's encephalitis was established 10 years after the onset of illness, when it was probably in its residual stage. The overall clinical symptomatology, along with the EEG and MRI scan data, were

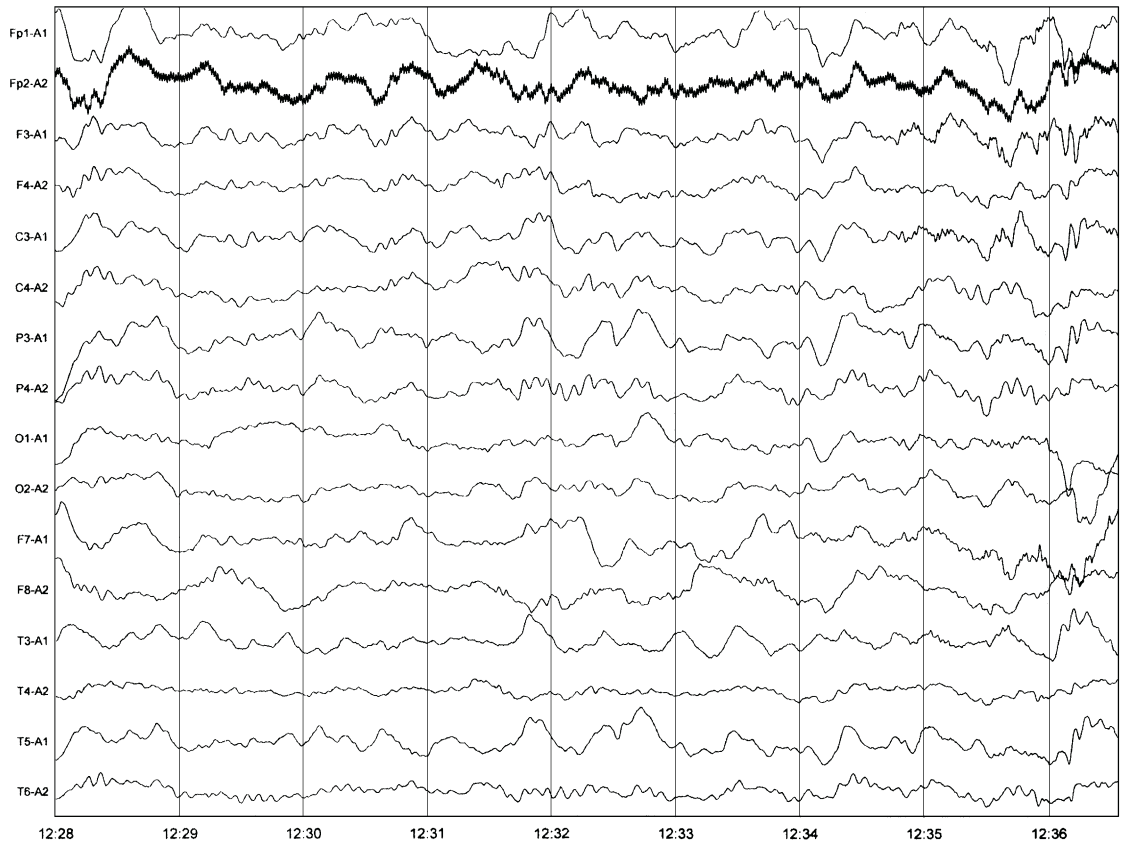

Fig. 6. EEG, patient G, June 18, 2010: Regional slowing of baseline activity in the left frontal-temporal-parietal areas, epileptiform activity as occasional sharp waves in the left frontal area.

entirely consistent with the international diagnostic criteria for Rasmussen's encephalitis [5]. The late diagnosis of the disease was associated with a number of features of this case: 1) the absence of *epilepsia partialis continua*; 2) the absence of any increase in focal neurological deficit (hemiparesis); 3) the appearance of new neurological symptoms (dysarthria, dysphasia) several years into the illness, which were interpreted as "progressive cortical deficit" in accordance with diagnostic criteria, though on the background of regression of motor disorders these were interpreted as indicators of "dissemination in space;" 4) the radiological syndrome of multifocal lesions to the white matter with the appearance of new foci, reminiscent of MS foci; 5) the frequent regression of some symptoms (perhaps delayed reactions to pathogenetic treatment, as is seen in chronic neuroinfections, such as neuroborreliosis); 6) the absence of hemiatrophy of the brain in the first 2.5 years of illness. MRI scans were not performed during the next seven years, so the dynamics of the corresponding changes in this period are unknown. Nonetheless, the diagnosis of Rasmussen's encephalitis could have been suspected relatively early, considering the structural lesions of only one hemisphere on repeat MRI scans and the corresponding lateralization of epileptiform syndrome and neurological deficit. Timely diagnosis (during the acute stage) is important in most cases of Rasmussen's encephalitis, as repeated short courses of immunotherapy during the active phase, along with long-term immunosuppressive treatment, should be performed with the aim of suppressing autoimmune inflammation and preventing progressive cerebral atrophy [6].

Thus, symptomatic epilepsy in demyelinating and inflammatory diseases of the CNS may be rare, but present serious diagnostic and therapeutic problems in neurological practice. Summarizing our data, the main features of treating patients of this type can be addressed:

1. A single epileptic seizure or episode of neurological dysfunction of presumptively epileptic nature in a patient with demyelinating or inflammatory disease of the CNS requires electroencephalography and brain MRI scans. Determination of disease activity with visualization of possible areas of structural brain damage responsible for epileptogenesis requires contrast agents to be used with MRI scans for assessment of post-contrast T1-weighted and/or diffusion-weighted imaging (DWI with assessment of ADC), along with DIR-GM impulse sequences to visualize pathological foci in the cortex.

2. In cases in which the only epileptic seizures develop in the absence of any preceding neurological disease, a brain MRI scan should be performed to exclude symptomatic epilepsy. MRI detection of multiple brain lesions requires a series of additional investigations for diagnostic precision, including CSF investigations for the presence of an infectious or immunologically mediated process.

3. Treatment of symptomatic epilepsy in demyelinating diseases should be provided in accordance with the ongoing type of seizures and the usual recommendations for selecting and prescribing AEA. If treatment is insufficiently effective and there is a suspicion of a direct relationship between seizures with exacerbations of the underlying process (frequent or serial seizures, status epilepticus, MRI data), then courses of treatment with corticosteroids given parenterally are indicated, and, if this is ineffective, reinitiation of pathogenetic treatment depending on the nature and severity of the underlying disease.

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