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# Различные исходы энцефалита, вызванного Herpes Simplex Virus (клинические и ЭЭГ наблюдения)

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# Different Fate of Herpes Simplex Encephalitis (Clinical and EEG Cases Report)

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## Резюме

Провели клинические и ЭЭГ-обследования 2 пациентов с острым энцефалитом, вызванным вирусом простого герпеса (ЭВВПГ): М. Б., 23-летняя женщина, получавшая лечение на дому по поводу тяжелого органического психосиндрома, постоянный уход за которой осуществляла медсестра, и Л. Й., 16-летняя пациентка, на 3-м году жизни перенесшая ЭВВПГ, который перешел в аутоагрессивную форму, напоминавшую энцефалит Расмуссена, с эпилептическим статусом в виде длительной парциальной эпилепсии. Проанализировали ранние и поздние исходы.

Данные ЭЭГ статистически обработали с использованием «спектрального анализа мощности» и трехмерного цветного картирования, позволяющего выявить топическую локализацию отдельных диапазонов частот ЭЭГ-кривых и измерить межнейронные связи в продольном и поперечном направлениях с помощью определения средней когерентности (показателя межнейронных связей).

На 9-м году жизни Л. Й. перенесла ветряную оспу с выраженными высыпаниями на коже и повышением температуры тела. При этом у нее выявили уменьшение высокоактивных изменений на ЭЭГ и клинической симптоматики, в том числе фокальной. Данное уменьшение произошло на фоне применения анестетика тиопентала и болюсного введения кортикостероидов, а также приема амантадина сульфата.

При осмотре во время самостоятельной ходьбы у Л. Й. обнаружили центральный монопарез правой нижней конечности, а также — 4–5 коротких миоклонических спазмов в суставах рук при приведении, в сочетании с непроизвольными выкриками, напоминающими крик осла, глубокими вдохами и выдохами. Больная находилась при этом в полном сознании. По данным МРТ выявили область гиперинтенсивного сигнала парасагиттально на левой стороне двигательного центра, по данным ЭЭГ — признаки эпилептогенной активности в области прилежащего рубца. По результатам сравнения последней ЭЭГ пациентки Л. Й. с ЭЭГ ее гомозиготной сестры патологической активности не выявили — записи были схожи.

Обе пациентки выжили на фоне длительного противовирусного лечения, интенсивной терапии, направленной на защиту нейронов головного мозга, эффект которой был доказан в динамике по данным классического и статистического анализа ЭЭГ.

Поздние исходы у обследованных пациенток были диаметрально противоположными. Пациентка Л. Й. окончила 9-ти летнюю среднюю школу с хорошими результатами. Пациентка М. Б. была посте-

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пенно мобилизована, несмотря на клинические признаки постэнцефалитной энцефалопатии с недостаточным ответом на нейролептики и седативные средства. После получения согласия родителей ее перевели в областную больницу.

***Ключевые слова:*** *ЭЭГ; энцефалит; спектральный анализ мощности; картирование мозга; HSV1; HSV2; энцефалит; вирус простого герпеса*

## Summary

We followed clinical and EEG examinations of two patients with herpes simplex encephalitis (HSE) in acute condition along with monitoring their early and late outcomes. Patients: M. B., 23-year-old female, who completed home treatment as a severe organic psycho-syndrome, reliant on nursing care, and L. J., now 16-year-old female patient, whose HSE in the 3rd year of her life went into auto-aggressive Rasmussen encephalitis-like condition with epileptic status in the form of Epilepsia parcialis continua (EPC).

The EEG signal was statistically processed using «power spectral analysis» with color maps 3D BM showing the performance of individual frequency bands topographically and the measurement of connectivity in longitudinal and transversal direction by means of the mean coherencies — indexes of connectivity.

On the 9th year of L. J. life when she overcame varicella with a significant eruption of the skin and high temperature the highly active EEG patterns were attenuated both graphically and clinically with a significant reduction in focal epilepsy. The latter was affected by a total thiopentotal anesthesia and bolus corticotherapy, as well as amantadine sulphate.

This patient exhibited central right lower limb mono-paresis in a selfstanding walk and 4–5 short myoclonic abduction cramps in arm joints associated with vocalized «hee-haw», deep inspiring and expiring in full consciousness. MRI proved hyperintense area parasagitally on the left side of the centromotor region and EEG with epileptogenic grapho-elements in adjacent scar. We compared the last sample of the EEG signal to the EEG patterns of her homozygous sister and found them identical with no pathological graphoelements.

These patients survival was the result of continuing anti-viral treatment, intensive medical and nursing care aimed to protect neural cells in the brain, the effect of which was longitudinally monitored by classic and statistical EEG signal analysis.

The late outcome of these patients was diametrically different. L. J. graduated from the 9-year primary school with good results. M. B. was progressively mobilized, despite the clinical signs of severe alterations of psychic sphere as a result of postencephalitic encephalopathy with insufficient response to neuroleptics and sedatives. After parents' agreement received she was transferred to the regional hospital.

***Keywords:*** *EEG, encephalitis, power spectral analysis, brain mapping, HSV1, HSV2, Herpes Simplex Encephalitis*

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## Introduction

Herpes simplex virus of Type 1 labialis causes meningo-encephalitis, which is usually located in the fronto-temporal area and is commonly haemorrhagic with poor prognosis and comparatively high lethality [1]. Herpes simplex — Type 2 genital infection causes aseptic recurrent Mollaret's meningo-encephalitis with fair prognosis [2]. Clinical characteristics include: headache, fever with seizures, and disorders of consciousness. Epilepsia parcialis continua — status epilepticus of focal motor seizures was usually identified in the 1980s as subacute / chronic viral encephalitis, caused by Eastern subtype tick-born arbovirus. Several viruses including herpes simplex virus-1 (HSV-1) served as etiological factors inducing non-specific grapho-elements in the EEG signals acquired from the area of centro-motor cortex of the contra-lateral hemisphere [1]. Localization of HSV-1 affected regions occurs in orbito-frontal and allocortical temporal areas and is associated with disorders of smell and taste, hallucinations, behavioral disorders, complex partial seizures, dysphasia, hemiparesis, hemianopsia. CT and MRI render a diagnostic support exposing haemorrhagic necrosis, confirmed by cerebrospinal fluid examination. Polymerase chain reaction (PCR) as a specific genetic proof of HSV-1 copies represents a helpful ancilliary inestigtion. Treatment includes antivirals including acyclovir, amantadine sulfate, amantadine chlorate. Acyclovir is admitted as a basic medication in i.v. infusion at 10 mg/kg for 1 hour in adults. Without this treatment, viral load leads to a rapid lethal outcome in approximately 70% of cases. Survivors suffer from severe neurological and psychiatric disorders [3]. Serological evidence is a slow but specific ancillary test, and the virological investigation represents another very slow test. Even with specific treatment, HSE is fatal in the 1/3 of cases, with severe neurological defects, and more than 50% patients survive. The survivors recover with mild neurological defects, only a small sample of survivors (2.5%) retain normal brain functions [4].

Many cases of amnesia originate in HSE [5]. Timely treatment in 48 hours of initial symptoms improves the chances of better results. Treated patients rarely have recurrent HSV-1 infection in a few

weeks or months. There is evidence that aberrant inflammation induced by HSV-1 may result in granulomatous inflammation in the brain that is sensitive to glucocorticoids [6]. Although HSV-1 infection is contagious, HSE itself is not contagious. Other viruses (HSV-6, varicella zoster virus-VZV, Epstein-Barr virus — EBV, cytomegalovirus — CMV, coxsackievirus, and others) can cause similar symptoms of encephalitis, and it even occurs more easily. In intensive treatment of HSE we apply stringent neuroprotective principles and treatments [7, 8]. Histopathologic analysis provides specific data on structural changes in the the brain, but these alterations are not critical enough to be considered as the only criteria enabling differential diagnosis between HSE and Rasmussen encephalitis [9–14].

One of the helpful screening methods useful for HSE diagnosis is electroencephalography (EEG). Brain structures generate EEG signal in intracellular (microtubules) and extracellular oscilators (electrical and mediator-controlled synapses) of hemispheric gray matter. Electroencephalogram is defined as an alternating type electrical activity that is recorded from the surface of the scalp and is taped by electrodes coated with conductive medium.

In the EEG analysis we used the Neuron Spectrum AM program, where we evaluated the EEG signal not only visually (classic approach), but also using power spectral analysis (topographic mapping of brain activity, the 3D brain mapping, BM). We finally use coherence as a conjunctivity index in color brain maps, where particular bipolar connections are evaluated by color lines. In the case study we analyze the EEG signal of two HSE patients as sporadically occurring inflammatory brain disease. For quantitative assessment of EEG we have been using power spectral analysis representing a powerful analytical tool that allows determining the spectrum or spectral power density of an EEG signal. The mathematical method extends the diagnostic possibilities of the medical doctor and extends his/her knowledge gained through the visual evaluation of the registered EEG signal.

Topographic brain mapping (3D BM) that visualises EEG analysis results in spatial «distribution — raster» of the brain electrical activity. The essence of 3D BM lies in encoding of numerical values of the signal into color scale by its iterative interpolation as well as in the areas, where the signal values is not measured. The distribution of the electrodes on the head is in the international 10/20 system. The use of 3D BM is of significance for those variables that are not directly within the analogue waves of the EEG signal in the viewed time window visible to a naked eye because they are interferentially hidden in another rhythm [15, 16]. The basal rhythms of the EEG signal are computed by signal filtration, coherence, or frequency, and are transformed, in a mysterious way, into fundamental brain functions — attention, multimodal coordination, conscious awareness. It is advertised to support the assumption that the physiological mechanisms responsible for the brain rhythms play crucial role in facilitatation of some cognitive operations [17]. They are either calculated from the signal and are not recognizable by the physician (frequency spectra, relative spectrum) when analysing the analogue EEG signals, or they are generated by recalculation of the frequency from the pairs of electrodes — coherence, that is relevant to the observation of brain plasticity — regeneration of cerebral activity after ischemic stroke, brain bleeding, or tumor post-surgery and other neurosurgical procedures. Detection of inflammation represents another important area of 3D BM in EEG application [18].

## Clinical Cases

M. B., a 23-year-old female patient, admitted at the neurological department of the regional hospital on 26/11/2017 with signs of psychomotor agitation-hyperactive delirium, amnesia, logorrhoea, nausea, high temperature, and headache. Upon admition, a contrast-assisted CT scan was executed with negative results. Lumbar puncture revealed possible serous neuro-infection (protein: 0.7 g / l, leucocytes 105/76% Ly), CRP below 5, Leu 14.3, FW 8 /16, pro-calcitonin 0.1, toxicology was negative. Within the therapy: cefotaxim 4g, acyklovir 500 mg, manitol 20%, tiapridal, alprazolam, diazepam. When she was admitted to the Clinic of Infectology and Travel Medicine of JFMED CU and UHM in Martin, the patient was soporous, GCS 8 points, non-cooperating, provided painful exclamation to various sounds, meningeal neck opposition was not present, ocular bulbs remained in the middle position, exhibited isocoria, miotic pupils, with no any other patterns of deficiency of cranial nerves. Nose and ears exhibited no spout, there was evidence of a regular heart beats, eupnoea, breathing was clean and vesicular throughout, no symptoms and signs of sudden abdominal event, permanent urinary catheterization showed clear urine, lower limbs were without swelling and signs of deep venous thrombosis. On admittance, the body temperature was 37.1°C, blood pressure 120/60, HR: 86 / min, $SpO_2$: 93%. The attending physician determined serous encephalitis syndrome on the admission. Based on this conclusion, empirical parenteral antiinflamatory treatment continued, and acyclovir, cefotaxim, anti-oedema treatment (dexamethasone, mannitol) were initiated.

MRI brain examination — native and post-contrast in T2, FLAIR demonstrated hyper-intensive cortical-subcortical bilateral frontal-inferior, temporal-anterior-medial regions, v. s. in herpes encephalitis. After administration of the contrast agent, the meninges were routed and enhanced frontal-temporal bilateral. The middle line structures were not shifted, and infratentorial structures were without morphologic changes in the brain tissue.

After receiving the patient on INF-ICU, we performed an electroencephalographic examination (fig. 1) using power spectral analysis (fig. 2). The records were evaluated in reference, transversal and longitudinal montages.

In the reference connection (fig. 1):

In some locations, especially in (CZ–C4), there is a continuous, long — lasting beta activity with a relatively low

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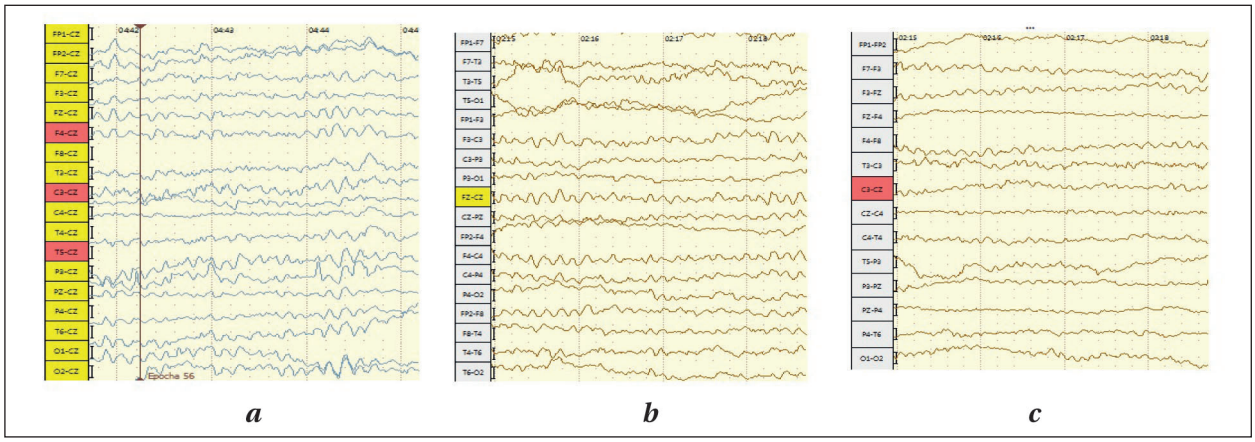



**Fig. 1. EEG, M. B., 23-year-old female patient.**
**Note.** *a* — the REF montage with the bilateral spindle of 6.5 Hz. theta activity and maximum AP in Cz-Pz with dispersion of delta waves. The grafo-elements are not positioned as continuous, long-lasting rhythms, but as short episodes or delta waves dispersion without the formation of epilepto-morphic or epilepto-genic complexes. *b* — the longitudinal connection shows similar grapho-elements in the EEG signal. *c* — the transversal connection shows the dispersion of theta and delta waves.

amplitude. In other connections (longitudinal and transversal wiring, fig. 1, *b, c*) delta activity (namely in fig. 1, *c*) with high amplitude and frequency of 3.5 Hz is present, and there is a low voltage fast activity in this EEG sample(LVFA). High performance theta (fig. 1, *b*), except for the rear temporal area on the right, indicates for the possible extinction of EEG theta rhythm focal point in the right posterior temporal region (fig. 2, *a – right*)

Further, the EEG examination was executed using power spectral analysis (figs. 1, 2). The records were evaluated in reference, longitudinal and transversal montages, and the results of the analysis in the last two montages were identical.

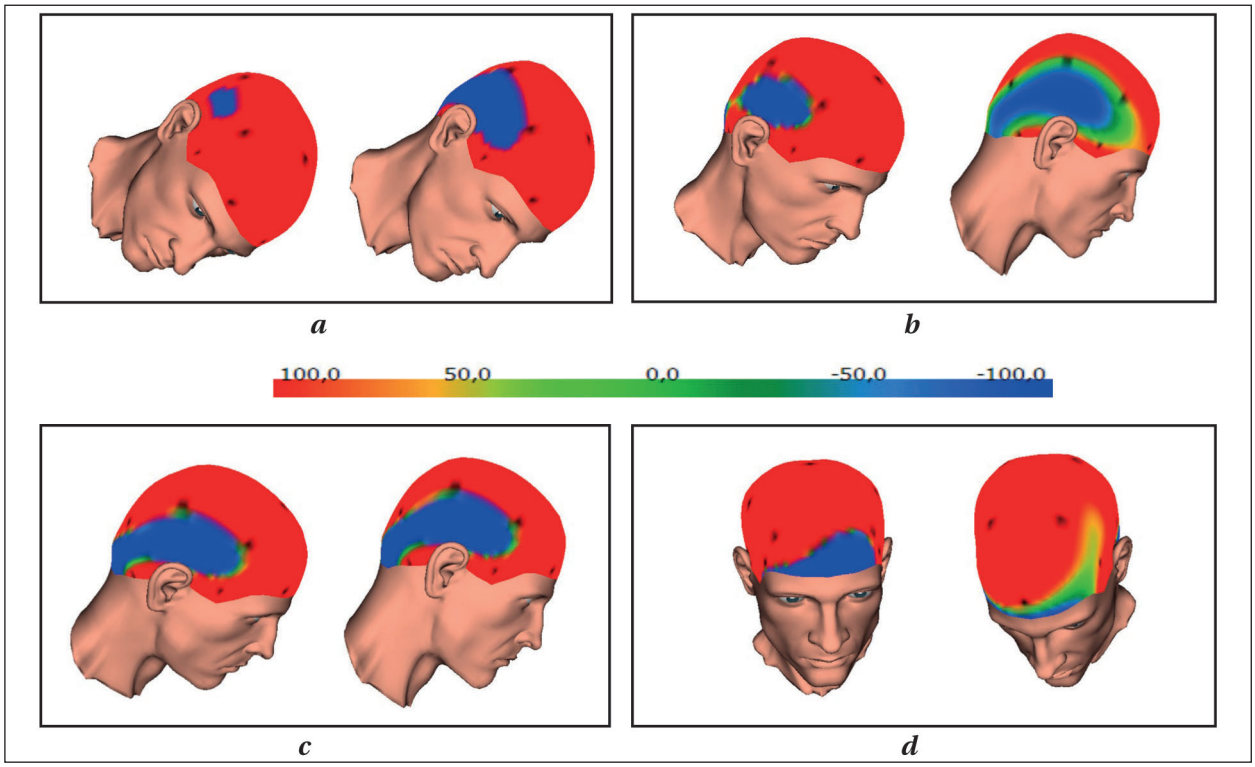
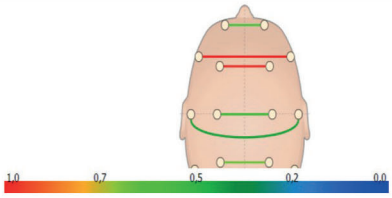
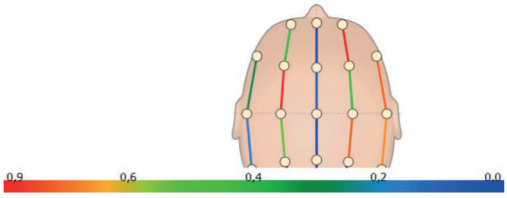
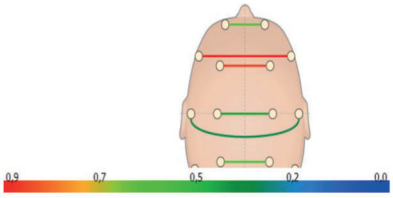
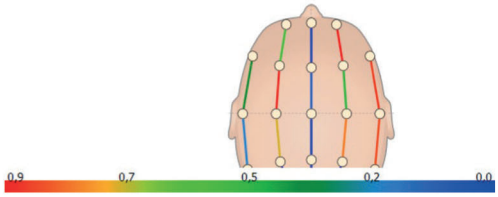
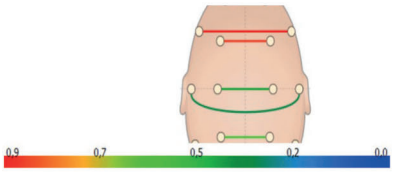
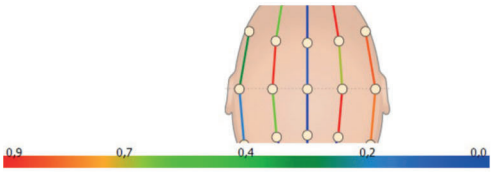
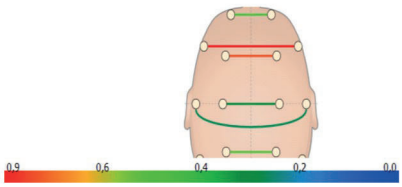
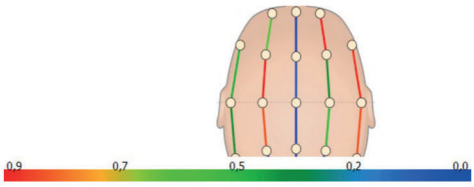
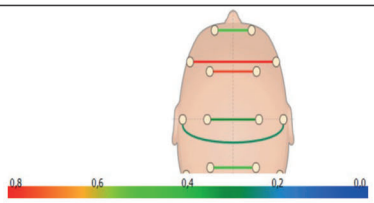
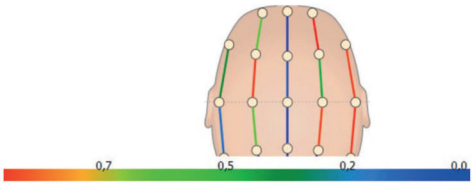
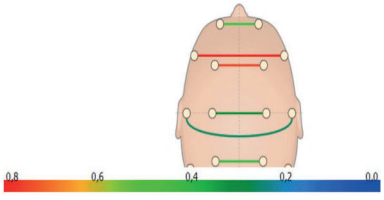
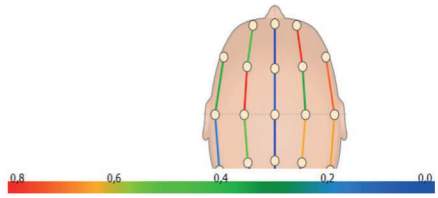



**Fig. 2. M. B., 23-year-old female patient, power spectral analysis.**
**Note.** *a-left* — REF montage. Total performance — power of the delta-rhythm (Closed eyes). High delta performance almost over the entire neuro-cranium except a small region in posterior temporal right. The color scale below the picture illustrates power. *a-right* — power of the theta-rhythm (Closed eyes). Extinction of theta activity backward temporally to the right does illustrate extinction focus structure. *b-left* — REF montage. Total performance — power of the alpha-rhythm with a defect in right posterior temporal region. *b-right* — performance of gamma rhythm with a wide defect in the right temporal region. *c-left* — REF montage. Total performance — power of the beta-LF-rhythm. *c-right* — performance of the beta — HF-rhythm. Both frequencies indicate simillar extinction in the right temporal regions. *d-left* — total power of beta HF rhythm in longitudinal montage. *d-right* — power of the gamma rhythm in the transversal montage.

**Table 1. Mean coherence in transversal (interhaemispheric) and longitudinal (anterior-posterior) connections, M. B., 23-year-old female patient.**

| Rhythms | Figurs in different connections | |
|---|---|---|
| | Transversal | Longitudina |
| Alpha |  |  |
| Beta HF |  |  |
| Beta LF |  |  |
| Gamma |  |  |
| Delta |  |  |
| Theta |  |  |

In the reference connection (fig. 1, *a*) in some localities, especially in CZ–C4, continuous long — lasting beta activity with a relatively low amplitude is present. In other connections (longitudinal and transversal connections fig. 1, *b, c*), delta activity (fig. 2, *a – left*) and desynchronized low voltage fast activity (LVFA) were present in some connections.

Coherences of EEG signal demonstrate connection between two points covered by two EEG electrodes. Quantitative EEG signal evaluation is presented in table 1 that demonstrates very praefrontal and centro-motor connections, whereas retro-rolandic and biparietal ones are lower in all frequency bands. There is a posterior decrease in connectivity of both haemispheres.

As it is seen in table 1, the decreased mean coherence in fronto-polar, parietal, and occipital regions is evident in any band (line green colour).

As it seen in table 1 interruption of connectivity is evident in left temporal region and in all vertex montages (blue colour lines). Light disconnections in praefronto-centromotor right haemisphere (green colour lines) and in centro-motor-parietal (right gamma rhythm, green colour lines) have become evident.

Follow-up of cerebro-spinal fluid (CSF) confirmed the progression of laboratory signs of neuroinfection. It is clear from the EEG record that the assumed inflammation is characterized by disseminated irritation and destruction signaling associated with a high-power theta frequency and the visible disappearance of theta rhythm in the right posterior temporal area without significant epileptogenic organization of the specific grafo-elements typical for HSV-1 encephalitis with no symptomatic epileptic seizures.

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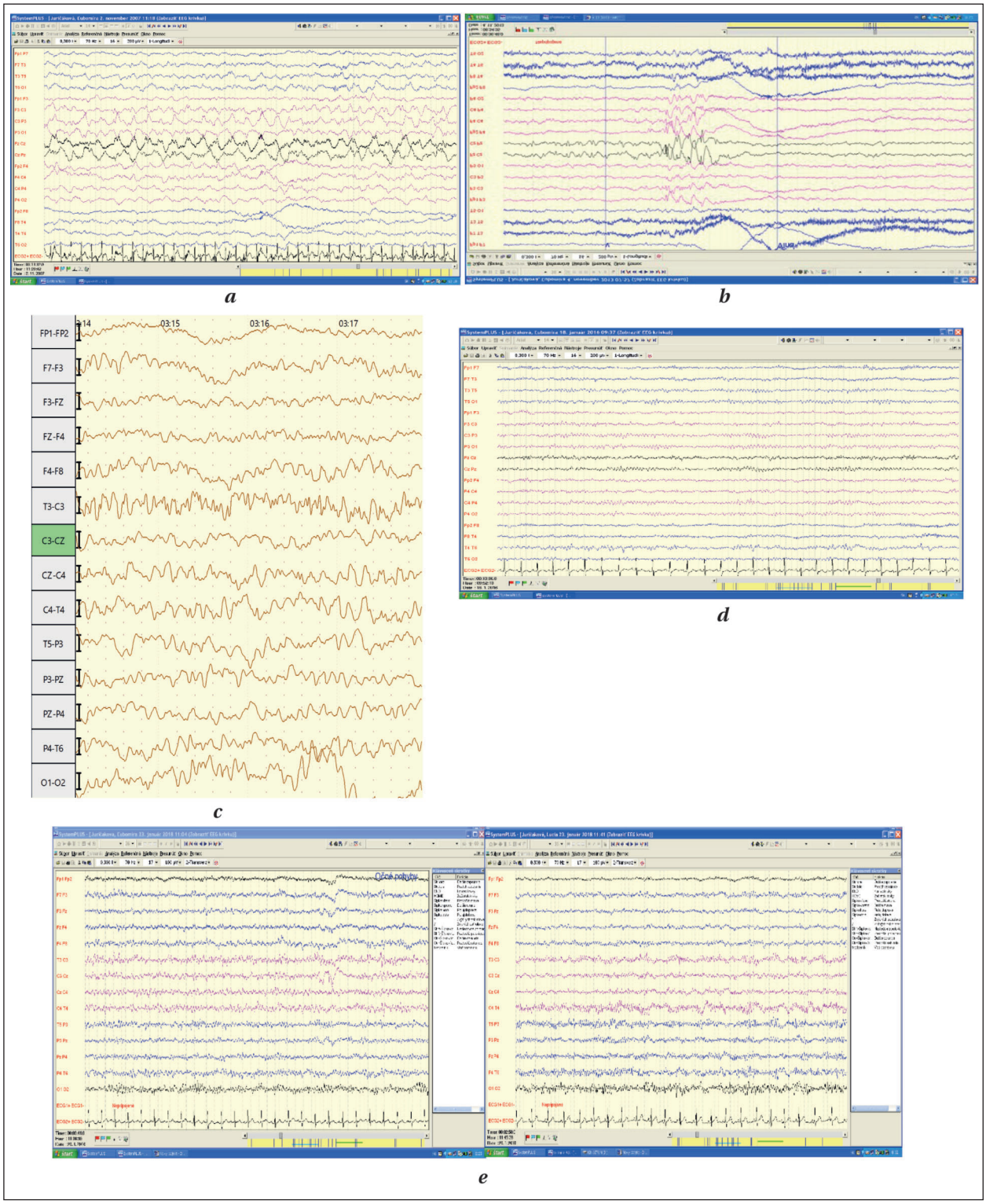


**Fig. 3. EEG, Patient L. J. and the healthy twin.**

**Note.** *a* — 4 -year-old, 2007, the 1st attack of HSV-1 (HSE): longitudinal montage with EPC status epilepticus (Koshevnikov) on the right half of the body. *b* — 9-year-old, epileptic discharges primary in vertex widespreaded bilateral parasaggital predominantly to left — transversal montage — 04. 11.2013. *c* — 9-year-old, after acute HSE, which provoked RLE. At the stage of VZV varicell-zoster infection and with traces of EBV, CMV in cerebrospinal fluid. Transversal montage with distinct focal activity of epileptogenic beta spikes and sharp theta waves in T3–C3, C4–T4 leadings, over time with Levetiracetam, Timonil-retard, Rivotril, but Phenytoin-free treatment — 14.06.2013. *d* — L. J. — 12-year-old, January, 2016, treatment with Phenytoin, Levetiracetam, Timonil retard (Rivotril omitted) — longitudinal montage. EEG signal free of pathologic morphs. *e* — L. J. — 14-year-old HSV1–RLE — left and L. J. — 14-year-old-right, her healthy homozygous sister, 23.01.2018.

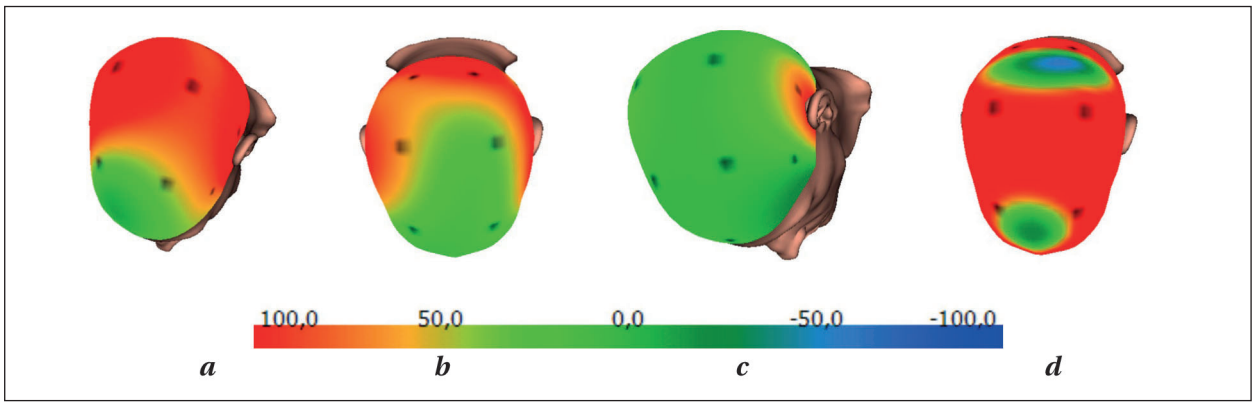


**Fig. 4. L. J, 9-years-old child patient, power spectral analysis, 3D BM of the EEG on the fig. 3 c, 4s lasting sample.**
**Note.** *a* — alpha-rhythm shows the dominance in the occipito-temporo-parietal region suggesting a lucid aware consciousness with closed eyes and psycho-relaxation. *b* — theta-rhythm dominates bilaterally temporally with occipital-raster penetration, suggesting localization of a posible epileptogenic aggregate. *c* — delta rhythm is delimited to the left small temporal region, but its power over the predominant part of the neurocranium is low — green colour. *d* — beta HF covers in 3D BM almost the entire neurocranium, except for the oval occipital defect and the round green defect frontal predominantly right.

The HSV-1 specific PCR assay confirmed the expectedly high 50,000 copies of HSV-1 DNA. The treatment of acute HSE including the bolus methyl-prednisone treatment, continued along with the acyclovir cure.

The patient was conscious at the beginning, but later became disoriented, without unambiguous sensoric-motor deficiency, with a marked psychomotor disorder requiring sedation with neuroleptics, physical fixation on the bed and repeated neurological and psychiatric counselling. Despite adjusting the supportive treatment, attempts to initiate any significant improvement failed. Only after 19 days of treatment, a followed-up CSF examination confirmed regression of HSV-1 in CSF, brain MRI confirmed intensive patterns of remaining inflammatory damage in frontal-temporal region of both hemispheres, with regression of oedema. Secondary bleeding in CSF, necrosis, and intra-cranial thrombosis were not confirmed. No HSV-1 DNA was detected on repeated CSF screening.

The patient was progressive mobilized, despite the clinical signs of severe alterations of psychic sphere as the result of postencephalitic encephalopathy with insufficient response to neuroleptics and sedatives. After parents' agreement received she was transferred to the regional hospital.

**The second patient with HSV-1 encephalitis: L.J., 14-year-old,** first admitted at 3 years old. It was a high-temperature disease in which seizures began to develop similarly to the Epilepsia partialis continua (EPC), with the status epilepticus and simple partial seizures on the right limbs (fig. 3, *a*). The EEG demonstrates epileptogenic and epileptomorphic graphoelements with a predominant specific focal discharges (left, parasaggital) and progressive paralysis of the right lower limb (RLL), later right upper limb (RUL), and finally light paresis of the left lower limb (LLL). This central triparesis was initially flaccid, without pathologic reflexes, with gradually increasing the spastic muscle tone and development of pathological reflexes to RUL and RLL representing Babinski tonic reflex. Foot and toe clonus on the right leg remained as a residue after EPC, but it gradually disappeared under continuous treatment with levetiracetam [19]. The phasic Babinski reflex was only weakly marked on LLL. We managed the status epilepticus after 11 days of thiopentotal anesthesia along with methylprednisone. Clinical picture and EEG changes were stabilized following discontinuation of general anesthesia and corticotherapy, daily epileptic Jackson seizures were gradually declining to become episodic with a tonic-clonic character.

Evaluation of serum and CSF for paraneoplastic and autoimmune encephalitis antibodies were negative as in a similar study of Castellano et al. 2017 [20].

Clinical data confirm the HSV-1 induced symptomatic — Rasmussen-like encephalitis (RLE) that was consisted with the continuation of clinical signs of epilepsia partialis continua, except that the LLL was also affected, i. e. one-haemisphere disorder was not fulfilled, which was typical for the type 2 RLE.

After a 6-year interval, the patient experienced high-density varicella (60.000 copies of varicella virus DNA were determined in CSF by PCR). HSV, EBV, CMV were of low density as determined by PCR in CSF. Treatment included Atb, Acyclovir, Levetircetam, Timonil retard, Rivotril (fig. 3, *b* — transverse montage) and after omitting Rivotril and adjusting for Phenytoin permanent epileptic seizures (EPC) ceased and EEG signal had changed (fig. 3, *d*, longitudinal montage).

At this time, the mother registered myoclonic twitches 20–30 times a day with the EEG correlate shown on EEG (fig. 3, *b*).

The last important picture of the 3D BM in EEG signal quantitative evaluation illustrates fig. 4, *d* for beta-HF-rhythm.

After omitting Rivotril and phenytoin deployment, the EEG image changed- normalized (fig. 3, *d*). EEG epileptic discharges and clinical myoclonic seizures completely disappeared for a 3-year interval.

When compared the EEG signal of the patient L.J., 14-year-old, with the EEG signal of her homozygous sister L.J., 14-year-old, the twin, it was similar in character to this signal as we know from our past observation of EEG single-twins (fig. 3, *e*).

MRI — T2 weighted axial image illustrates a structural morphologic changes — parasaggital scars-the fig. 5, *a*. MRI –T1 weighted saggital section showed dysplastic — microgyric structure in the fig. 5, *b*.

Anterior-posterior and transversal coherences, such as connectivity indices, are promising quantitative param-

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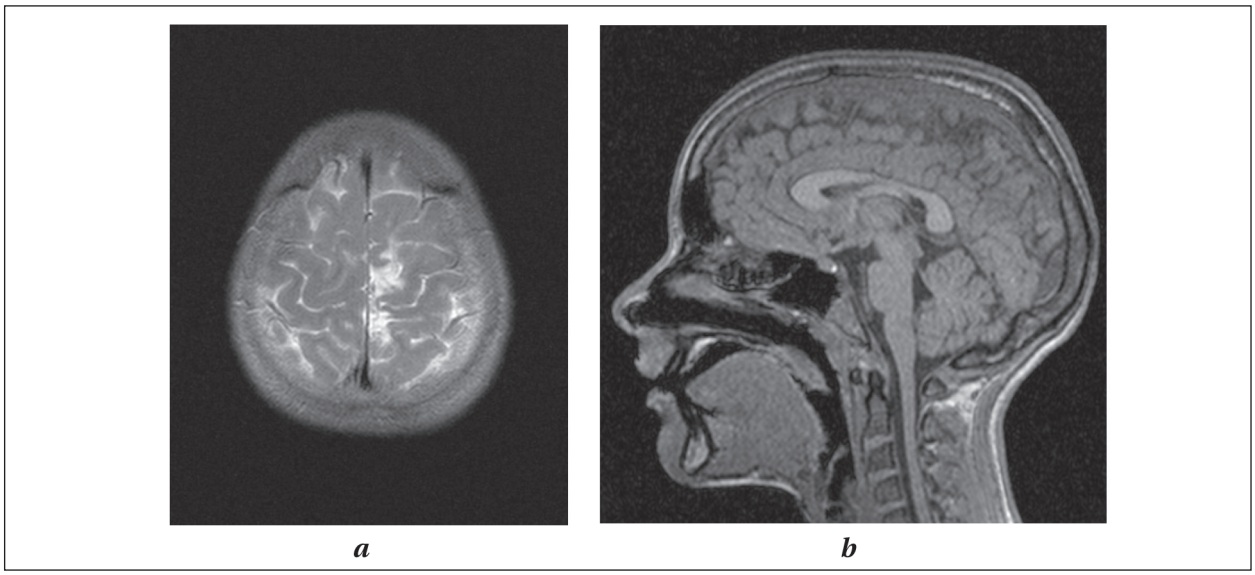



**Fig. 5. L. J. 9-year-old child patient, MRI pictures.**
**Note.** *a* — the MRI — T2 weighted image in axial section depicts the hyperintens signal representing post-inflamatory parasaggital, centromotor, and retro — rolandic scar structure to the left. *b* — the MRI — T1 weighted image in sagittal section shows the medial area of the left haemisphere with dysplastic gyrification in the centromotor and partly also in the post — rolandic region. HSE has gone into an auto-aggressive form of RLE. Dysplasia of cortical structures is a characteristic associated affection in Rasmussen encephlitis.

eters of the EEG signal. They may show the state of connectivity via preformed pathways, full or partial split brain interhemispheric disconnection, complete or partial interruption of the anterior-posterior connections (table 2).

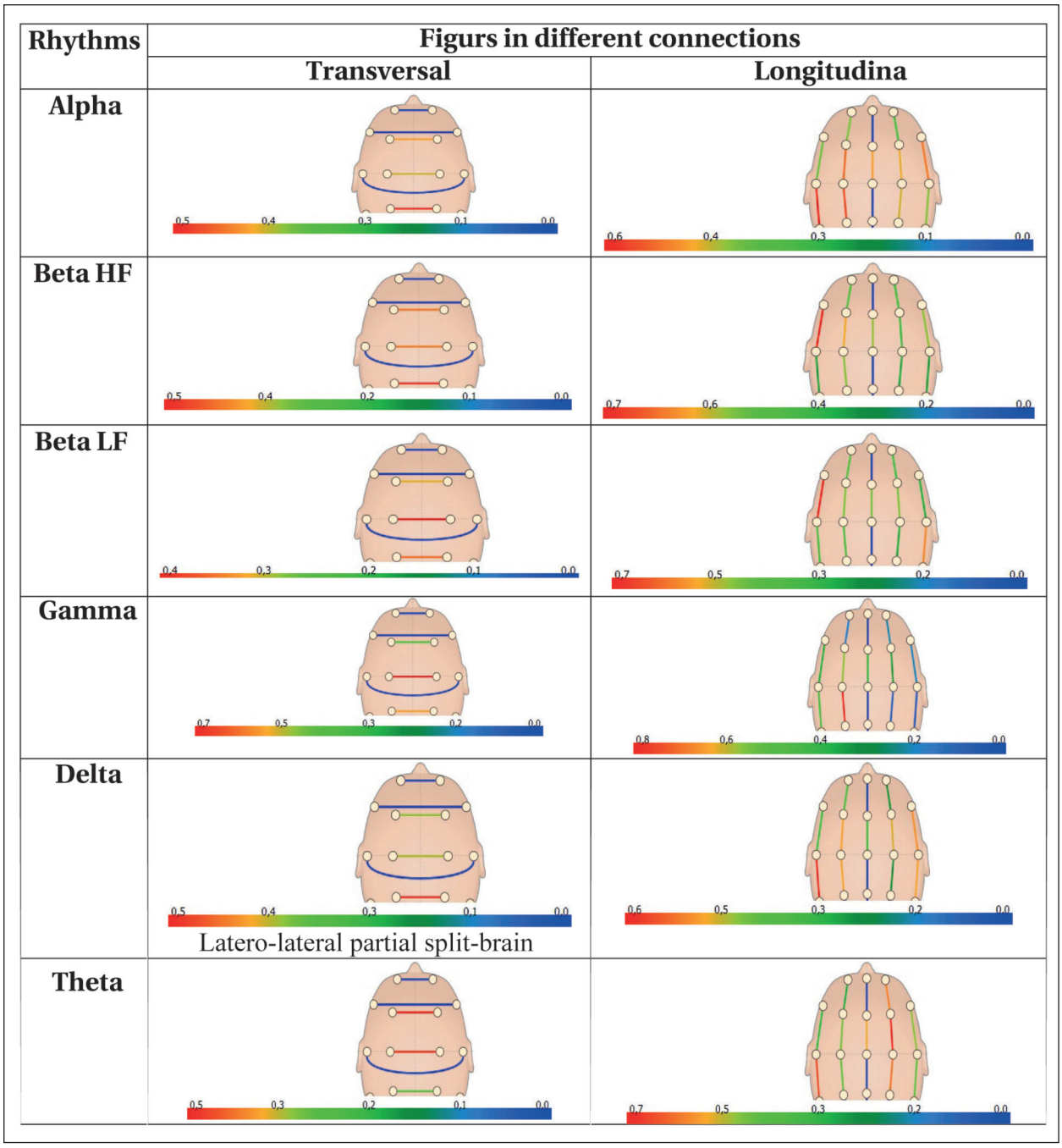
**Total rating of EEG signal registered in 14.06.2013:** The relatively irregular EEG signal (fig. 3, *c*) is dominated by a 6–7Hz sharp theta wave focus in T3–C3, C4–T4 connections, where the theta rhythm controls the occipital and bitemporal areas in the 3D BM raster image (fig. 4, *b*). In short periods, this activity changes into sharp theta waves with a frequency of 6–7 Hz, AP 60 microvolts within a time window of 4 seconds. Spindle beta (fig. 3, *c*) appeared in T3-C3. 3D BM alpha activity (fig. 4, *a*) suggests a lucid consciousness. The relatively irregular EEG signal (fig. 3, *c*) is dominated by a 6–7Hz sharp theta wave focus in T3–C3, C4–T4 connections, whereas the 3D BM raster image demonstrates that the theta rhythm controls bitemporal and the occipital areas (fig. 4, *b*). The Delta rhythm has a high power in a small area at the rear left with low power in the rest of the neurocranium (fig. 4, *c*). In table 2, the blue colour lines show disconnecions and green colour lines demonstrate decreased connections in transversal and longitudinal montages.

**Conclusion of EEG and clinical examination (14.06.2018):** There is a permanent temporal focus of theta rhythm on the left T3–C3, and on the mirror C4–T4 montage in transversal montage. The epileptomorphic oscillations of theta 6–7 Hz and beta HF spikes in the centro-temporal region on the left persist (fig. 3, *c*). In 3D BM — raster picture theta waves spread across bitemporal and occipital region (fig. 4, *b*) meanwhile beta-HF oscillation spread across almost total neurocranium (fig. 4, *d*). Epileptomorphic activity around the MRI of proven postencephalitic scar in MRI-T2 weighted pictures and dysplasia of the left paramedial centromotor and retrorolandic landscape in MRI-T1 were manifested daily by clinically short myoclonic convulsions consisting of upper limbs abduction, associated with vocalized «hee-haw», deep inspiring and expiring at full consciousness (fig. 3, *b*). Very short myoclonia occurs 4–5 times a day. ANCA auto-antibodies are non-constantly positive in the blood of family members. Therefore, the anti-epileptic therapeutic formula including Levetiracetam 250–0–250 mg, Timonil retard 150–0–150 mg, and Phenytoin 3×100 mg has been found successful treatment option for the described case.

## Discussion

The course and long-term development of HSE in the two patients, adult M. B., 23-year-old and (now) 16-year-old L. J., are characterized by living with different consequences [1]. We attribute this to a consistent intensive care for all the circumstances of aggressive HSV encephalitis, including the EPC status epilepticus (Kozhevnikov') of patient L. J., who is currently 16 years old. Her post-HSE development focused mainly on the paracentral region of the left hemisphere (fig. 5, *a*) with scar, dysplastic gyrification, and active focal synchronic epileptic and myoclonic bursts, presumably due to auto-aggressive glial cell lesion, as evidenced by fig. 5, *b*, and possibly related to familial psoriatic autoimmune burden. The probable underlying auto-aggressive nature of inflammation is likely to activate astroglia, namely varicocytes, and help to form an epileptogenic aggregate, as shown by Castellano et al. 2017 [20]. In physiological circumstances, varicocytes assemble functional modules for cognition, especially for complicated multi-modal memory tracks. Under the pathologic conditions, astrocytic assemblance may construct an epileptogenic aggregate. In the first case this circumstance did not apply, MRI native and post-contrast in T2, FLAIR demonstrated hyperintens cortico-subcortical bilateral fronto-inferomedial, temporo-anteromedial regions, in

**Table 2. Mean coherence in transversal (interhaemispheric) and longitudinal (anterior-posterior) connections, patient L. J., 9-year-old child.**




clinical assumption — v.s. HSE of origin in negative autoaggressive familial history. HSE mechanism caused an increased signal that was enhanced after contrast, and, therefore, probably no epileptic seizures have been observed so far because HSV-1 does not attack astroglia-varicocytes, while autoimmune mechanisms may impact alterations of these cells in the latter case with auto-immune familial history.

MRI findings, specifically unihemispheric focal cortical atrophy, with or without T2 signal changes and caudate head hyperintensity or atrophy, represent the second diagnostic criterion [21]. Variability of MRI findings, even rarely including bilateral changes, in both pediatric and adult populations, appears to be the rule rather than the exception [20]. Dual pathology, which includes cortical dysplasia and RE, is a well documented phenomenon [22–29]. Based on this multiplicity of MRI findings, we conclude that coexistent cortical dysplasia should not distract from a diagnosis of RE and advanced imaging analyzes should be performed when a diagnosis of RE is suspected [20].

EEG observations, specifically unihemispheric slowing with or without epileptiform activity and unilateral seizure onset, represent the third diagnostic criterion ([20].

In described case with bilateral occurrence of epileptomorphic graphoelements and unilateral occurrence of epileptic convulsions during EPC (patient L.J., 16-years-old), the epileptic play begins as epileptic status — EPC (Kozhevnikov'). After thiopental anesthesia, methylprednisone bolus, and amantadine sulphate treatment, the permanent epilleptic activity is converted into episodic myoclonic activity (30–40 convulsions per day), with bilateral-synchronic spikes in vertex electrodes dispersed to the left-right centromotor and parietal electrodes of discharge episode of 1–1.5 seconds duration. Then, the interictal EEG signal is normalized after adding Phenytoin to Levetiracetam, Timonil-retard, omitting rivotril and amantadine sulphate, and EEG signal becomes similar to the one of the healthy monozygotic twin. Later, however, despite the effective antiepileptic treatment, clinically short myoclonic seizures start that associate with vocalized «wheezing», inhaling and exhaling in full consciousness. Such myoclonia occurs 4–5 times a day.

Adult M. B., 23-year-old had no such graphoelements and, therefore we do not assume an auto-aggressive substrate induced by HSV-1 as a powerful mechanism activating microglia and astroglia — varicocytes. In this case, the pure cytopathic effect induced by HSV-1 probably destroyed by the activation of apoptosis with possible epileptogenic aggregate, and, therefore, the epileptic syndrome did not develop. Histopathological examination of biopsy material from the RE site is theoretically possible, but the procedure seems to be impractical due to its invasive and traumatic character. Histopathologic inclusion criteria may contain T-cell dominant encephalitis with activated microglia, and exclusion criteria presumably include the presence of numerous parenchymal macrophages, B cells, plasma cells, or viral inclusion bodies [20]. Much like the MRI and EEG observations, the histopathology of RE appears more complex than the diagnostic criterion definition. Again, findings may be bilateral, and multiple pathologies, namely cortical dysplasia, may co-exist with RE. Given these observations, some authors suggest that concomitant pathology not distract from a diagnosis of RE [20, 13, 14]. Furthermore, given the multifocal nature of RE pathology and potential absence of pathology in mild disease or during prodromal periods, some authors would not encourage the use of focal cortical biopsy to aid in RE diagnosis [9, 10, 20, 11, 12]. We have also followed this principle, and currently we do not recommend focal brain biopsy.

As treatment options, we used antiepileptics in triple combination, corticoid bolus, thiopental anesthesia. We plan epileptosurgical consultation and immunomodulation (natalizumab?) in the case of RE. Interestingly, 2×250 mg levetiracetam resulted in gradual diminishing the right foot clones, although according to our long experience in other etiological affections of the CNS, such intense hyper-reflexive phenomenon is successfully managed only with high doses of baclofen. Therefore, we should apply intrathecal baclofen administration with the aid of permanent pump.

We followed published data [30] on quick attenuation of the foot clone by bolus levetiracetam at a dose of 2.000 mg i. v. in RE patients. In the second case (patient M. B., 23-year-old, with HSE symptoms), treatment that included neuroleptics at maximum sedative doses provided not satisfactory results in the form of severe organic psychosyndrome, however, with no neurological focal motor or sensory deficiencies.

## Conclusion

Two patients diagnosed with HSE encephalitis demonstrated two different patterns. One case (M.B., 23 years of age) was acutely developed HSE associated with infero-fronto-temporo-medial destruction without epileptogenic aggregate. After 3 months of intensive treatment at UHM in Martin, this condition was matured toward severe organic psychosyndrome without motor or sensory neurologic deficiencies. Psychomotor restlessness of the patient required neuroleptic sedation and physical immobilization. The EEG image consisted of the dispersed occurrence of theta and delta graphoelements not organized in epileptogenic complexes specific for seizures. EEG alterations represented non-specific disorder of the oscillators in the temporo-medial portion of the Sommer segment that included hippocampus, amygdalum, and orbitofrontal cortex as substrates of organic psychosyndrome. Absence of specific epileptogenic patterns on EEG demonstrated low risk of epileptic seizures in the first patient.

In the second case (L.J., 16-year-old girl), the acute HSE began as a status epilepticus in the form of EPC-Kozhevnikov' on the right limbs and left lower limb followed by central triparesis, with Babinski tonic reflex and a foot clone on the RLL. Thiopental anesthesia, bolus corticosteroids, amantadine sulphate 3×200 mg stopped the status epilepticus and led to the formation of generalized clonic convulsions lasting 1–2 seconds at a brief frequency as bilateral synchronic episodes of EEG bursts. Such clinical convulsions repeated for 30–40 times daily. Presumably autoagressive in nature, the Rasmussen-like encephalitis in patient possesed fluctuating course of seizures. Following the administration of Phenytoin 3×100mg to the Levetiracetam, Timonil-retard and omiting Rivotril together both clinical and EEG seizure activities disappeared. They re-appeared recently as brief myoclonic seizures of the upper limbs in the form of abduction convulsions with a frequency of 3–4 times per day. The latter patterns associated with vocalized «hee-

haw», deep inspiration and expiration at full consciousness. This patient attended a 9-year primary school with good results and her last EEG patterns were similar to the EEG patterns of L. J. 16 level of a homozygous twin. Psychological evaluation, however, demonstrated that, in contrast to her homozygous sister, the patient scores were decreased by about 30%. We continue to follow her development for a prolong time.

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