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Non-paraneoplastic limbic encephalitis associated with antibodies to potassium channels leading to bilateral hippocampal sclerosis in a pre-pubertal girl

Judith Kröll-Seger[1], Christian G. Bien[2], Hans-Jürgen Huppertz[1]

[1] Swiss Epilepsy Center, Bleulerstrasse 60, 8008 Zurich, Switzerland
[2] Department of Epileptology, University of Bonn, Bonn, Germany

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ABSTRACT – Limbic encephalitis (LE) is increasingly recognized as a precipitating factor of adult onset temporal lobe epilepsy frequently associated with bilateral hippocampal damage. So far, clinical data in children are rare and only comprise paraneoplastic forms of LE. We describe a 13-year-old pre-pubertal girl in whom non-paraneoplastic LE was diagnosed according to diagnostic criteria proposed by Bien and Elger (2007). The girl presented with a subacute syndrome comprising memory impairment, affective disturbances, and refractory temporal lobe seizures. Serial MRI scans demonstrated an initial temporomedial swelling with T2/FLAIR signal increase progressing to bilateral hippocampal atrophy within seven months. Two years after onset of symptoms, antibodies to potassium channels were found to be slightly elevated. Immunosuppressive therapy with steroid-pulses was followed by a transient reduction of seizure frequency, even though this was started more than two years after onset of first symptoms. However, extended immunotherapy was refused by the patient's parents, so no full assessment of the treatment response was possible. In conclusion, this case shows that non-paraneoplastic LE leading to mesial temporal lobe epilepsy is not restricted to adult patients. The proposed diagnostic criteria therefore should be adapted for paediatric patients. Patients may profit from immunosuppressive therapy even when it is started at a late stage with already overt hippocampal sclerosis.

Key words: non-paraneoplastic limbic encephalitis, pre-pubertal girl, mesial temporal lobe epilepsy, bilateral hippocampal sclerosis

Correspondence:
J. Kröll-Seger
Swiss Epilepsy Center,
Bleulerstrasse 60,
8008 Zurich,
Switzerland
<judith.kroell@swissepi.ch>

Drug resistant temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS) is considered to be the most frequent epilepsy syndrome. It constitutes a heterogeneous group with respect to etiology and clinical course. In the majority of cases, TLE-HS manifests before the age of 20 years. Frequently, there is an initial precipitating injury (IPI) followed by a latent

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period before the onset of habitual seizures. In a retrospective clinico-pathological analysis of 172 surgically treated patients with TLE-HS, 39% of patients presented with an initial precipitating injury (prolonged and complex febrile seizures in 57%) before epilepsy onset (Blümcke *et al*. 2007).

In contrast, adult-onset TLE-HS is rare. For almost 50% of such patients in a recent series, the precipitating cause was either definitively or possibly linked to limbic encephalitis (LE) (Bien *et al*. 2007, Bien and Elger 2007). LE is clinically characterized by subacute onset of short-term memory impairment, psychiatric disturbances and seizures. Evidence of a peripheral tumour or demonstration of 'well characterized' onconeural antibodies directed to intracellular antigens, *e.g*. anti-Hu, anti-Ta or anti-Ma, lead to the definitive diagnosis of paraneoplastic LE (Dalmau and Rosenfeld 2008, Graus *et al*. 2004, Gultekin *et al*. 2000). In contrast, patients with LE and antibodies against voltage-gated potassium channels (VGKC), that present on neuronal surfaces, only rarely develop cancer (Pozo-Rosich *et al*. 2003, Thieben *et al*. 2004, Vincent *et al*. 2004) and usually have a favourable prognosis (Bien and Elger 2007, Thieben *et al*. 2004, Vincent *et al*. 2004). Recently, patients with the clinical features of LE and antibodies that predominantly react with the neuropil of the hippocampus, are directed against cell surface antigens beyond VGKCs, *e.g*. the N-methyl-D-aspartate receptor (Dalmau *et al*. 2007), have been described. These occur in both, paraneoplastic and non-paraneoplastic forms of LE (Bataller *et al*. 2007). In children, a few cases of paraneoplastic LE have been published (Carr 1982, Gregorios *et al*. 1987, Meyer *et al*. 1995, Rosenbaum *et al*. 1998). So far, however, there are no reports concerning the existence of non-paraneoplastic LE as the underlying cause of TLE-HS in children.

Case report

A 13-year-old girl presented on 27th February 2004 with a seven day history of a subacutely evolving syndrome of mnestic deficits associated with behavioural problems (affective disturbances, behavioural regression), weight loss and focal seizures (epigastric aura, flush, oro-alimentary automatisms, alternating left and right-sided cloni with or without eye-blinking). Memory impairment was severe and already disabling in everyday life (e.g. the girl could not remember time and date) and she was unable to dress or undress without help (apraxia). There was no fever. Cerebrospinal fluid (CSF) investigations showed normal cell count and protein content.

Initial MRI demonstrated bilateral swelling with T2/FLAIR signal increase of both amygdaloid nuclei and hippocampi with left-sided predominance. An additional signal increase was found in the left claustrum and insular region (*figure 1*, first row; enlarged sections through the hippocampi are shown in *figure 2*). Seven weeks later, the swelling was slightly regressive in the amygdaloid nuclei and clearly regressive in the hippocampi (*figure 1*, second row) and the T2/FLAIR signal increase appeared especially pronounced in the endfolium of the left hippocampus (*figure 2*, second row). Seven months after disease-onset, MRI demonstrated no more swelling but bilateral hippocampal atrophy with T2/FLAIR signal increase more prominent on the left side (*figures 1 and 2*, third row). At this time signal increase of the left claustrum and insular region appeared slightly decreased. Within the next two years MRI findings did not change further (*figure 1*, fourth and fifth row).

Daily psychomotor seizures persisted under the following anticonvulsive drugs, given in mono- or add-on-therapy: oxcarbazepine (30 mg/kg bw/d), valproic acid (26 mg/kg bw/d), levetiracetam (31 mg/kg bw/d), topiramate (7.5 mg/kg bw/d) and clobazam (0.5 mg/kg bw/d). EEG seizure patterns showed independent seizure onsets in the following regions: 1) left frontal, 2) left temporal or left fronto-temporal, and 3) right temporal.

Neuropsychological testing performed eight and 24 months after disease-onset revealed severe persisting deficits of verbal and non-verbal episodic memory. Verbal memory was assessed with the Verbal Learning and Memory Test (VLMT), a standardized German version of the Auditory Verbal Learning Test (AVLT) by Rey (Helmstaedter *et al*. 2000). Concerning verbal learning capacity and loss after delay, the patient only achieved results more than two standard deviations (SD) below the mean values for age. Figural memory was assessed with the Complex Figure of Rey (Spreen and Strauss 1998). Results were more than three SD below the mean scores for age.

The diagnosis of non-paraneoplastic, VGKC antibody associated LE was made two years after onset of first symptoms according to the diagnostic criteria suggested by Bien and Elger (2007) *(table 1)*. At this time CSF studies showed normal albumin, but elevated IgG and oligoclonal bands. All tests for neurotropic infectious agents (Cytomegalovirus, Epstein-Barr Virus, Human Immunodeficiency Virus Type 1, Herpes Simplex Virus Type 1, Varicella Zoster Virus, Measles, Mumps, Parvovirus-B19, Enterovirus, *Borrelia burgdorferi*, Toxoplasma, and Yersinia) were negative. There was no evidence of other antibodies (anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies, antinuclear antibodies, double stranded DNA antibodies, antineutrophil cytoplasmic antibodies) including the "well characterized" onconeural antibodies *(table 1)*. Thyroid hormones were normal.

The level of VGKC antibodies, assessed for the first time two years after onset of first symptoms, was low positive (157 pM, normal < 100 pM; *Prof. Dr. Angela Vincent, Department of Clinical Neurology Institute of Molecular*

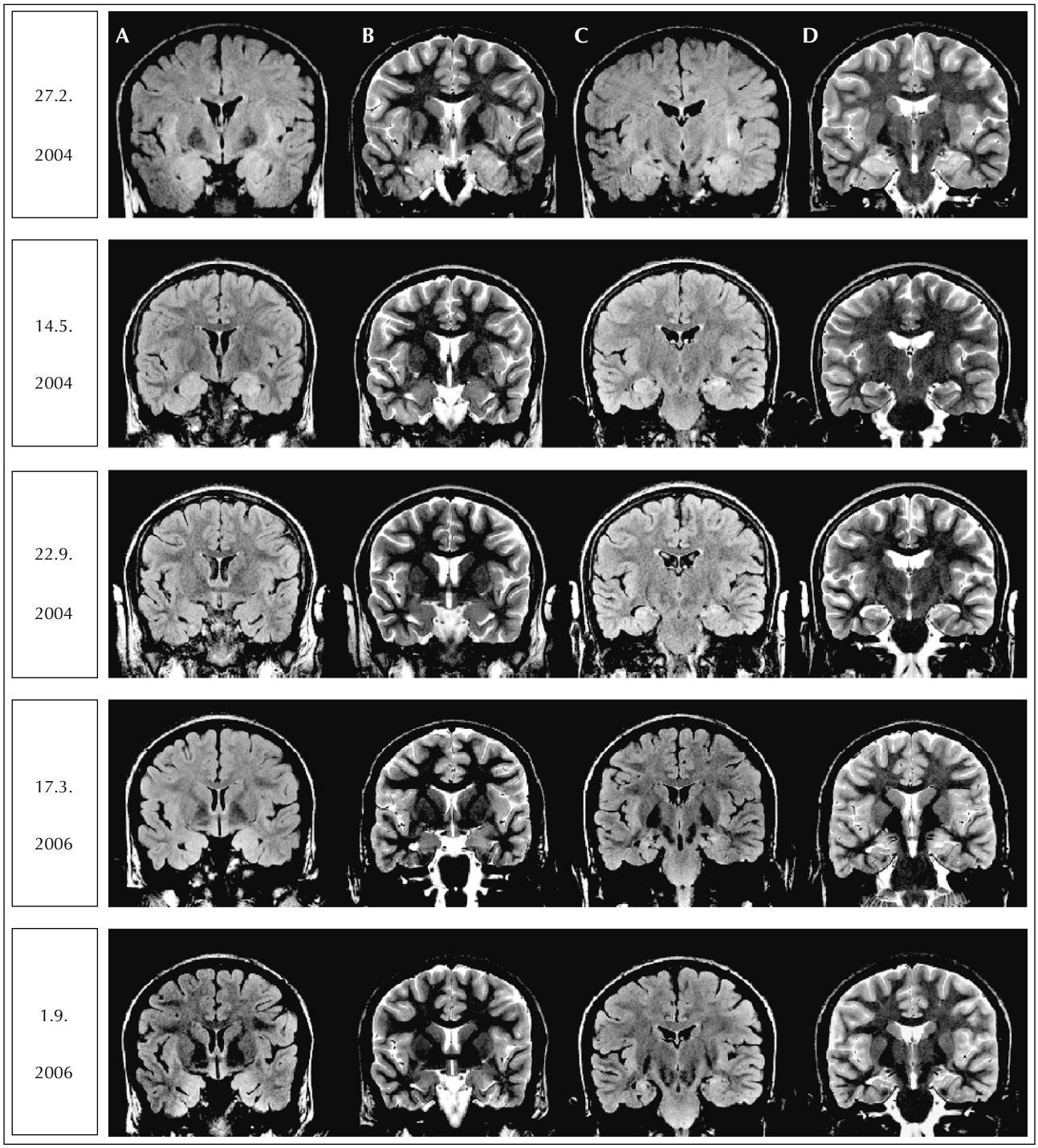

Figure 1. Serial coronal brain MRI sections through amygdala (**A**, **B**) and anterior hippocampal body (**C**, **D**) of the presented 13-year-old girl diagnosed with non-paraneoplastic, VGKC antibody positive limbic encephalitis. **A** and **C** contain FLAIR (= fluid attenuated inversion recovery)-weighted images, **B** and **D** T2-weighted images. The MRI scans show a rapid progression of an initial temporo-medial swelling with T2/FLAIR signal increase to bilateral hippocampal atrophy within seven months.

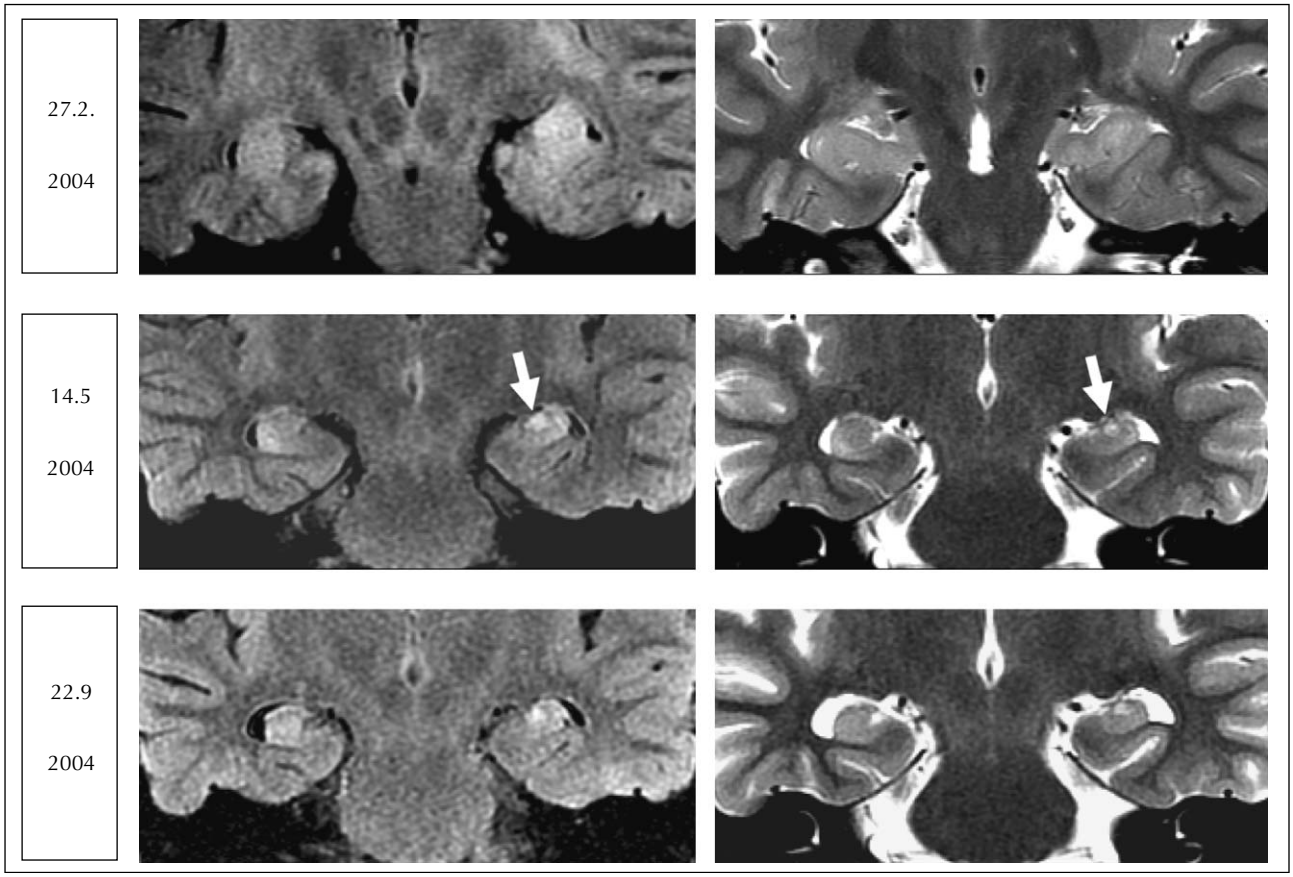

Figure 2. Enlarged sections of coronal FLAIR-weighted (left column) and T2-weighted (right column) images depicting the changes in the hippocampi in the first seven months after disease onset. The blow-up shows that on the left side the FLAIR/T2 signal increase is pronounced in the hippocampal endfolium (white arrows).

Table 1. Diagnostic criteria for limbic encephalitis (paraneoplastic and autoimmune non-paraneoplastic forms) proposed by Bien and Elger (2007).

Recent onset (< 5 years) clinical ''*limbic*'' syndrome in adulthood	At least one of the following three: Disturbance of episodic memory Temporal lobe seizures Affective disturbance, typically loss of inhibition and lability of mood
Plus 1 of the following four:	
Tumor	Demonstration within 5 years of onset of neurological symptoms
Auto-antibodies	One of the following (in serum, if not otherwise stated): ''Well-characterized'' antibodies antibodies: Hu antibodies Ma/Ta antibodies CV2/CRMP5 antibodies[1] Amphiphysin antibodies Voltage-gated potassium channel antibodies NMDAR heteromer antibodies[2]
Brain MRI	Otherwise unexplained temporo-medialT2/FLAIR signal increase
Histopathology	Lymphocytic–micronodular encephalitis affecting mainly the temporo-medial structures Histopathologically no indication of other primary pathology like stroke, tumor, posttraumatic scar, neurodegenerative disorder

[1] CRMP, collapsing response mediator proteins.
[2] NMDAR, N-methyl-D-aspartate receptor.

Medicine, John Radcliffe Hospital, Oxford, Great Britain). Regarding the presence of tumours, abdominal ultrasound and gynaecological examination were performed and showed no abnormalities.

The patient received an immunosuppressive therapy with steroid-pulses (intravenous methyl prednisone 3 x 500 mg/d during 3 days every 4 weeks). Due to her severe mnestic deficits the patient was not capable of keeping seizure charts reliably and there was also evidence that seizure frequency was underestimated by the patient herself. Therefore long term-EEG monitoring was considered the only objective parameter for assessing responsiveness to steroid pulses. Two pre-treatment, long-term EEGs were recorded. For the first recording, seven months before immunosuppressive treatment, five focal seizures with a left temporal seizure pattern were recorded over 24 hours. Only two of the five seizures were reported by the patient herself. In the second recording, performed immediately before the first steroid-pulse, three focal seizures and one subclinical EEG seizure pattern were recorded during 24 hours. Again, only one seizure was noticed by the patient. After the third steroid-pulse there was no manifestation of seizures and only one subclinical EEG seizure pattern during an EEG monitoring period three times longer (72 hours). Nevertheless without apparent reason, the parents refused to continue steroid-pulses and did not approve neuropsychological re-testing. Six months later, the patient again suffered from frequent daily seizures and newly evolving psychiatric co-morbidity (atypical anorexia nervosa).

Discussion

Proposed diagnostic criteria for LE (Bien and Elger 2007) are currently restricted to adult patients. The presented case fulfilled clinical, neuroradiological and auto-antibody criteria of non-paraneoplastic, VGKC antibody associated LE but was, however, presented at pre-pubertal age. The search for an underlying malignancy had to be adapted to the patient's age-dependent individual risk profile. With respect to age at onset, clinical course, and laboratory investigations, abdominal ultrasound and a gynaecological examination were considered adequate for tumour search. Furthermore, extensive serologic investigations were performed to exclude an infectious or parainfectious pathogenesis or the association with a possible autoimmune endocrine dysfunction or vasculitis.

Concerning the search for LE-associated auto-antibodies, VGKC antibodies were unfortunately not assessed at the onset of limbic symptoms. However, ab levels were low positive two years after onset of symptoms supporting the diagnosis of VGKC ab-associated LE. From studies in adult patients, a decline in VGKC antibodies over time, with and even without immunosuppressive treatment, is recognised (Buckley *et al.* 2001, Vincent *et al.* 2004). Thus, it can be hypothesised that VGKC antibodies were higher at disease onset. There are also reports of low to intermediate positive VGKC ab titres in patients with long lasting drug-resistant epilepsy (Majoie *et al.* 2006, McKnight *et al.* 2005). However, data concerning VGKC antibody titres over time in these patients is missing, and the subgroup of children and adolescents in these reports differ in three aspects from the presented case: no history of a subacute or acute limbic encephalitis-like syndrome, no mesiotemporal hyperintensities on MRI and long disease duration (mean 28.4 years) at the time of positive VGKC antibodies tested (Majoie *et al.* 2006, McKnight *et al.* 2005).

The temporal evolution of hippocampal oedema to HS-TLE also seems to be a special characteristic of LE (Urbach *et al.* 2006). In the present case, serial MRI scans demonstrated a rapid progression of an initial swelling of temporo-medial structures with T2/FLAIR signal increase to bilateral hippocampal atrophy within seven months. This is in accordance with the clinical course described in adult patients (Bien *et al.* 2007). Furthermore, with respect to clinical course and pattern of hippocampal damage, there seems to be an additional analogy with the case vignette presented by Bien *et al.* (2007), where histopathology of the sclerotic hippocampus confirmed MR signs of endfolium sclerosis (severe neuronal cell loss of the hippocampal subfields CA4 and CA3, whereas sectors CA1 and CA2 were relatively spared).

Concerning possible alternative explanations for the MRI course described above, there are qualitative and quantitative MRI studies of the hippocampus in children with prolonged febrile seizures (PFS) or status epilepticus showing an initial hippocampal oedema, however in contrast to the case presented here, hippocampal signal increase resolved within days (Scott *et al.* 2002). Although longitudinal MRI studies of children with PFS demonstrated a significant increase in hippocampal volume asymmetry over time, hippocampi did not meet the criteria for HS and there is usually a free interval of several years between a PFS or an IPI and the onset of epilepsy (Blümcke *et al.* 2007, Scott *et al.* 2003).

LE associated with VGKC antibodies apparently responds well to early-onset immunosuppressive therapy. Clinical and neuropsychological improvement has been observed to correlate with a reduction in antibody levels (Vincent *et al.* 2004). In the present case immunosuppressive treatment was started two years after onset, *i.e.* relatively late, with MRI already demonstrating bilateral hippocampal atrophy. Nevertheless, the patient showed a significant reduction of seizure frequency. This suggests that epileptogenicity was not only related to hippocampal scarring but also to an ongoing active immune-mediated process.

In conclusion, non-paraneoplastic LE as a precipitating factor of mesial temporal lobe epilepsy is not restricted to adult patients. The proposed diagnostic criteria (Bien and Elger 2007) therefore should be adapted for paediatric patients by lowering the age limit of 20 years and adjusting the protocol for tumour search. There seems to be a characteristic temporal evolution with rapid progression of hippocampal oedema to HS-TLE in LE which was also observed in this pre-pubertal girl. Patients may profit from immunosuppressive therapy even when it is started at a late stage with already overt hippocampal sclerosis. □

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