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Neurosyphilis and paraneoplastic limbic encephalitis: important differential diagnoses

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Sirs: A 34-year-old previously healthy heterosexual man with a history of alcohol and tobacco abuse was admitted to hospital after a first epileptic seizure. Neurological examination was unremarkable. Lumbar puncture was performed the same day with the following results: 4 cells/mm^3, protein 953 mg/l. Non-contrast CT was normal. EEG showed generalized slowing and epileptiform discharges. At first, symptomatic epilepsy in the context of alcoholism was suspected. During the following days, repeated complex partial seizures developed. The patient was disoriented, anterograde and retrograde memory were severely impaired. On the 4th day, MRI showed a contrast-enhancing (T1-) hyperintense signal alteration in the left medial temporal lobe on FLAIR and T2-weighted images (Fig. 1a). Repeat CSF-analysis showed 22 cells/mm^3, protein 952 mg/l, and positive oligoclonal bands. Serum/CSF tests for HSV 1/2, VZV, HIV 1/2 were negative. HHV-6-Ab titer in serum was 1:20 (IgG). VDRL in serum was positive, titer 1:8, in CSF 1:4. Quantitative TPPA-test in serum was 1:81920, in CSF 1:524288. *Treponema pallidum* IgG-Western Blot was positive in serum and CSF. Neurosyphilis (NSP) was diagnosed and IV penicillin treatment at a dose of 3 × 10 million units/d for 20 days was initiated. (Note: US Centers for Disease Control and Prevention recommended treatment for NSP [18]: penicillin G 18–24 million units/d administered as 3–4 million units IV every 4 hours or continuous infusion for 14 days).

Because of the MRI findings suggestive of limbic encephalitis [7, 12], paraneoplastic limbic encephalitis (PLE) was considered as a differential diagnosis. Anti-neuronal antibodies (anti-Amphiphysin, -Hu, -Ri, -CV2, -Ma2) were negative. Whole body F-18-FDG-PET showed a focal hypometabolism in the left medial temporal lobe and a circumscribed area of increased tracer uptake in the left upper lung (Fig. 1b). Thoracic CT correspondingly showed a hyperdense lesion of 1.6 cm in the left superior pulmonary lobe, suspicious of carcinoma. Wedge resection of the left superior pulmonary lobe was performed. Histopathological analysis showed a demarcated severe chronic inflammation with fibrosis (non-caseous degeneration). *Treponema pallidum* PCR was negative. There were no signs of malignancy.

Under continuous anticonvulsant therapy no more seizures occurred. The patient's state subsequently improved. However, after 8 months of follow up the patient still suffered from generalized cognitive slowing, impaired anterograde memory- and executive functions. Repeat MRI showed atrophy of left medial temporal lobe structures.

Although NSP has become rare in industrialized countries [9], it has to be considered in a variety of neuropsychiatric disorders. PLE is another infrequent CNS disorder, which manifests itself in the presence of an – initially frequently occult – malignancy. Patients with

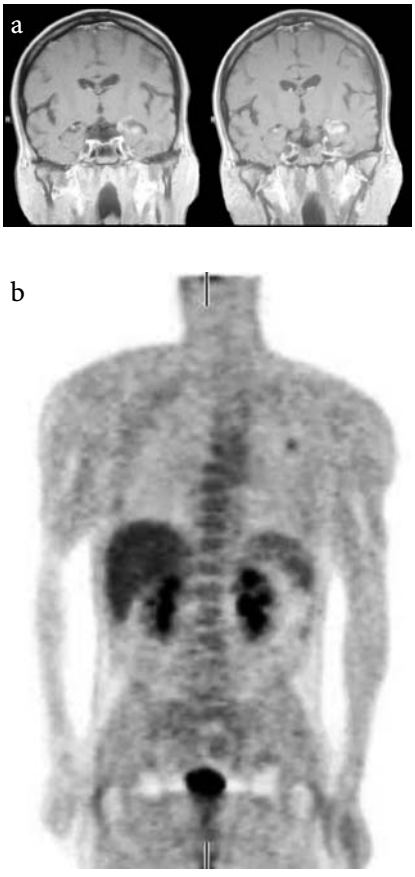

Fig. 1 **a** T1-weighted MRI in the coronal plane showing a contrast enhancing lesion in the left hippocampal formation. **b** Whole-body FDG-PET scan; coronal plane. Circumscribed, pathologically increased glucose metabolism in the left superior pulmonary lobe. Correspondingly, thoracic CT showed a hyperdense lesion of 1.6 cm, suspicious of a peripheral lung carcinoma (not shown)

PLE can harbor anti-neuronal antibodies, most often anti-Hu or anti-Ma2, which, however, are not obligatory [11]. Because of their unspecific or atypical clinical course, the spectrum of differential diagnoses of both diseases is wide. Particularly NSP has always been considered "the great imitator". Nevertheless, to our knowledge these entities have never been reported as direct differential diagnoses.

Clinical hallmarks of PLE are memory dysfunction, epilepsy, and psychiatric abnormalities [17]. The

same is true for our patient and certain previously reported patients with NSP. However, predominant medial temporal lobe involvement seems to be rare in NSP, since there are only anecdotal case reports of this particular variant in the MEDLINE database [1–6, 8, 14, 15, 19–21, 23] (Table 1). Furthermore, since reversible temporal lobe MRI abnormalities have been reported also in the context of par-

Table 1 Overview of the previously published patients with NSP and isolated or prominent medial temporal lobe involvement demonstrating a close similarity of clinical, neuroimaging, and laboratory findings as compared to PLE (*CE* contrast enhancement; *ea* epileptic activity; *gs* generalized slowing; *l* left; *mv* meningovascular; *nd* not done or no data available; *neg* negative; *pa* parenchymal; *pos* positive; *r* right; *WM* white matter)

Author	Number, age, and sex of patients	Symptoms and signs	Acuity of symptoms	MRI – Sequence and side of medial temporal findings	MRI – CE	MRI – Additional lesions	MRI – follow-up	EEG	CSF-protein [g/l]	CSF-cells [1/mm^3]	Serum VDRL RPR [titer]	CSF VDRL [titer]	Type of NSP
Ances et al. [1]	1; 41, m	memory impairment, epilepsy	acute	T2 l	nd	lateral temporal lobe l	nd	ea	1.17	43	1:32	1:16	nd
Angus et al. [2]	1; 34, m	disorientation, agitation, aphasia	subacute (3 days)	T1	yes	leptomeningeal enhancement	nd	ea	0.94	26	1:32	1:2	mv
Bash et al. [3]	1; 50, m	disorientation, memory impairment, epilepsy	subacute (3 months)	T2, FLAIR r > l	no	none	regression of hyperintensities, atrophy of temporal lobe structures r (4 months)	gs	0.87	19	1:64	1:16	mv
Berbel-Garcia et al. [4]	1; 47, m	disorientation, memory impairment, personality changes	slowly progressive (24 months)	T2	nd	lateral temporal lobe, frontal lobe r	regression of hyperintensities	nd	0.64	5	1:64	1:64	pa
Blanco et al. [5]	1; 46, m	apathy, memory impairment	slowly progressive (12 months)	T2 l = r	nd	temporal pole, insula, subcortical WM l = r	normalization	gs	1.18	140	1:16	neg	mv
Denays et al. [6]	1; 51, f	disorientation, memory impairment	acute	FLAIR l > r	nd	none	nd	ea	0.46	23	nd	nd	pa
Fujimoto et al. [8]	1; 41, m	disorientation, memory impairment	subacute (4 months)	T2, DP l = r	nd	caudate nucleus l, thalamus r	regression of hyperintensities (1 month)	nd	1.45	122	1:16	nd	pa
Lauria et al. [14]	1; 62, m	aphasia, hemiparesis, epilepsy	acute	FLAIR r	yes	caudate nucleus, gyrus cinguli, inferior frontal lobe r	atrophy of temporal lobe structures r (4 months)	nd	nd	5	pos	pos	pa
Marano et al. [15]	1; 48, m	memory impairment, epilepsy	acute	T2, DP r	no	basal frontal lobe r	regression of hyperintensities, atrophy of temporal lobe structures r (1 month)	nd	0.63	12	pos	pos	mv
Scheid et al. (current report)	1; 34, m	disorientation, memory impairment, epilepsy	acute	T2, FLAIR l	yes	none	atrophy of medial temporal lobe structures l (4 months)	ea gs	0.95	4	1:8	1:4	pa
Silberstein et al. [19]	1; 37, m	cognitive decline, memory impairment, deafness, epilepsy	slowly progressive (24 months)	FLAIR l > r	no	frontal lobe, insula l > r	nd	gs	1.43	32	1:128	1:128	pa

Table 1 *Continued*

Author	Number, age, and sex of patients	Symptoms and signs	Acuity of symptoms	MRI – Sequence and side of medial temporal findings	MRI – CE	MRI – Additional lesions	MRI – follow-up	EEG	CSF-protein [g/l]	CSF-cells [1/mm^3]	Serum VDRL RPR [titer]	CSF VDRL [titer]	Type of NSP
Szilak et al. [20]	1; 55, m	disorientation, confusion, memory impairment, epilepsy	acute	T2, FLAIR l	nd	subcortical WM	nd	ea	0.71	79	1:64	1:8	mv
Vojvodic et al. [21]	1; 45, m	mental confusion, memory impairment, epilepsy	slowly progressive (14 months)	T2 l = r	nd	none	nd	nd	0.53	9	1:32	nd	nd
Zifko et al. [23]	1; 35, m	memory impairment, depression	slowly progressive (2 years)	FLAIR l = r	nd	hippocampal and frontal atrophy	unchanged (12 months)	nd	nd	nd	neg	1:2	pa

tial status epilepticus [13], epilepsy has to be discussed as a confounder in the assessment of medial temporal lobe abnormalities in NSP, at least in the 10 patients of Table 1 with clinical or EEG evidence of epilepsy. In addition, it is interesting to note that the majority of these patients (8/10) had an acute or subacute onset of symptoms, whereas 3 of the remaining 4 patients without seizures had a slowly progressive course of the disease. It therefore could be speculated that the etiology of medial temporal lobe abnormalities might differ in NSP with and without epilepsy.

The pathogeneses of the MRI findings are unknown, both in PLE and in the reported variant of NSP. In the latter, several authors regard them as meningovascular [2, 3, 5, 15, 20]. However, the imaging abnormalities do not reflect a vascular territory and neuropathologically, arteritis is usually seen in large and medium-sized blood vessels in NSP [10]. The hypothesis of parenchymal syphilis is thus more convincing. Contrast enhancement may be observed in both disorders and is no criterion of differentiation (Table 1).

It is noteworthy that despite the frequent association of AIDS and syphilis, neither our not any of the previously reported patients has been tested HIV-positive. In analogy to the assumed autoimmune origin of PLE, this observation may indicate that a competent immune response is a prerequisite for the development of non-tumorous medial temporal lobe damage.

This case report demonstrates the possible complexity of the differential diagnostic procedure. FDG-PET has been reported to be useful in the diagnosis of paraneoplastic neurological syndromes [16]. However, it must be emphasized that FDG-PET findings are unspecific and might lead to wrong conclusions. Our observation therefore supports the conclusion of a current study that FDG-PET results should be interpreted with caution in patients without antineuronal antibodies [22].

In conclusion, neurosyphilis has to be excluded if paraneoplastic limbic encephalitis is suspected, and vice versa.

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