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Epilepsy in vacuolating megalencephalic leukoencephalopathy with subcortical cysts

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Vacuolating megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a disorder characterised by acquired macrocephaly, developmental motor delay of varying degrees, slowly progressive cerebellar and pyramidal signs, and initially preserved intellectual function. More than 60% of the published cases had epileptic seizures.

In this study, we analysed the seizures and EEG findings of nine patients with MLC. Six patients (66.6%) with moderate to severe neurological impairment had epilepsy, four with partial and two with generalised seizures. The EEG of five epileptic patients revealed epileptogenic foci over the temporal, frontal and parietal regions with variable predominance during waking and sleep. The facilitation of spike-and-wave paroxysms by eye closure, by intermittent photic stimulation and by hyperventilation were determined in four patients. Four patients also showed abnormalities in the background activity. In conclusion, we think that epilepsy is a significant component of MLC compared to the other leukodystrophies. The elucidation of the underlying molecular defect may explain the unusual pathogenetic relation between this leukoencephalopathy and the associated seizures.

Key words: epilepsy; EEG; leukoencephalopathy; cysts; megalencephaly; white matter.

INTRODUCTION

Vacuolating megalencephalic leukoencephalopathy with subcortical cysts (MLC, OMIM 604004) was described by Van der Knaap *et al*. in 1995 and recently mapped to chromosome 22q tel[1,2]. This disorder can be caused by mutations in MLC1 gene, but locus heterogeneity has been suggested also[3,4]. The main clinical features are acquired macrocephaly during the first year of life, developmental delay of varying degrees, slowly progressive cerebellar and pyramidal signs and initially preserved intellectual function. Cranial magnetic resonance imaging (MRI) shows distinct abnormalities of the white matter with diffuse high signal and swollen appearance on the T2-weighted images, and subcortical cysts localised mostly antero-temporally that are particularly evident on proton density and fluid-attenuated inversion recovery images (FLAIR)[5–10]. More than half of the published cases had epileptic seizures. The frequency of epilepsy seems to be a peculiar feature of this leukoencephalopathy compared with others. In this study, we analysed the seizures and electroencephalographic (EEG) findings of nine patients with MLC and reviewed the published literature.

METHODS

Six of the nine patients were epileptic, ages varying between 5 and 12 years. All cases had typical MRI abnormalities with diffusely hyperintense white matter on T2-weighted images and subcortical cysts [Fig. 1(a)–(c)]. All had megalencephaly. Each patient had one or more EEG while awake and/or asleep. Hyperventilation (HV), intermittent photic stimulation (IPS), eye opening and closure were routine activations, except in three very young patients who could not hyperventilate. Two electroencephalographers analysed a total of 17 EEG recordings independently.

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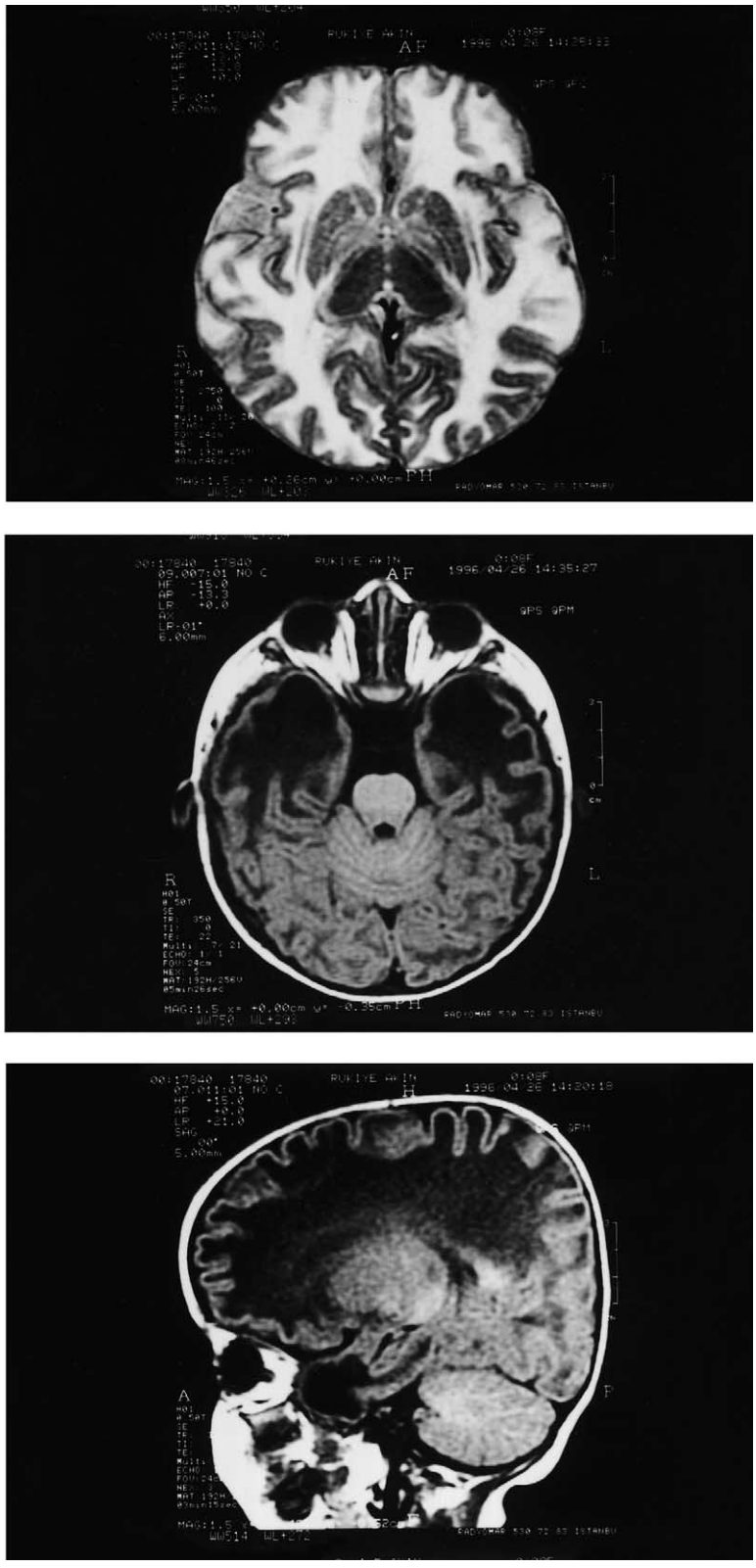


Fig. 1: (*a*) Axial T2-weighted image of Patient 1 showing diffuse white matter involvement with swelling; (*b*) axial T1-weighted and (*c*) sagittal T1-weighted images showing cysts on frontal and temporal regions.

The following parameters were analysed for each EEG recording: regularity of the background activity; responses to HV, IPS and eye closure; presence of focal epileptogenic activities, their tendency to generalise; presence and symmetry of the sleep spindles and K-complexes. Seizures were classified according to the Commission on Classification and Terminology of the International League against Epilepsy 1981[11].

RESULTS

All patients were younger than 12 years and six (two female, four male) had epilepsy (Table 1). Two children had only generalised seizures whereas the others had partial seizures with secondary generalisation (Table 1). Ages at the onset of seizures ranged between 2.5 and 4 years. The seizures were precipitated by minor trauma in four. The frequency of the seizures ranged from 1 to 10 per year. Relatively severe neurological involvement and developmental delay were present in three patients, two had seizures resistant to medical treatment.

One epileptic patient who had partial epilepsy had a normal EEG and two patients had normal EEGs before the onset of seizures. The epileptogenic foci had temporal, frontal and parietal predominance with migratory changes in waking and sleep. The other findings were facilitation of spike-and-wave paroxysms by eye closure (in three), by IPS (in three) and by HV (in two) (Fig. 2). Generalisation of those discharges was seen in four patients during NREM sleep. The sleep spindles were unusually scarce in two and absent in one patient, all of whom also had epileptiform discharges. Asymmetry of the spindles was evident in a single patient. The K-complexes were unusually scarce in one patient. There were abnormal beta and theta rhythms in the background activity of four patients. Three young patients without epilepsy had nearly normal development and neurological status. Their EEGs were also normal.

ILLUSTRATIVE CASE REPORT

Patient 2

A 12-year-old boy was born to a first degree consanguineous Turkish couple after an uneventful pregnancy and delivery. Macrocephaly was the presenting symptom. Head circumference was 51.5 cm at 9 months and 60 cm at 12 years of age (clearly above the 97th percentile). He walked at 14 months and talked in simple sentences at 24 months. He had six tonic–clonic seizures precipitated by minor head trauma starting at the age of 4 years. He received valproate therapy. He attended primary school, however, his performance declined in reading and arithmetic. The neurological examination at 7 years of age revealed mild mental retardation, dysarthria, bilateral dysmetria, dysdiadochokinesia, hyperactive deep-tendon reflexes and colour blindness. At 9 years of age, he developed prominent ataxia preventing walking without assistance, and had bilaterally positive Babinski signs, with no remarkable change on follow up.

The first EEG at 2.5 years of age was normal. The second EEG at 7 years of age, showed normal background activity. There were bilateral spike-and-wave discharges predominant on the right occipito-parietal and temporal regions becoming generalised during HV and by eye closure. During sleep, the epileptiform discharges shifted to the left frontal and right temporal regions with occasional generalisation. No sleep spindles were present in NREM sleep. The third EEG at 9 years of age showed similar findings, including generalised discharges during IPS. The last EEG at the age of 11 showed bilateral beta activity with fronto-central predominance, in addition to the previous findings [Fig. 3(a) and (b)]. In the last two sleep recordings, very rare sleep spindles and K-complexes were present.

An MRI at 7 years of age showed diffuse involvement of the white matter with flattened gyri. Multiple cysts were present in the subcortical white matter, most prominently in the left frontal and right temporal lobes.

The sister of this patient (Patient 1), 5.5 years old, also had MLC and epilepsy. At age 3 years, she had partial and secondarily generalising seizures precipitated by minor head trauma, followed by brief periods of regression in language and motor performance. Interestingly, her EEG recordings showed no activation with HV, IPS and eye closure in contrast to her brother. However, bifrontal abnormal beta activity and shifting epileptiform discharges in sleep were findings in common with her brother.

DISCUSSION AND CONCLUSIONS

Epileptic seizures may occur as an early manifestation in most of the grey matter diseases and are considered rare in white matter diseases[12]. Up to now, the precise pathogenesis of the epileptic seizures in the leukodystrophies has not been fully understood, and the EEG features have not been well described[13].

In metachromatic leukodystrophy, epileptogenic discharges occur rarely[14], but may be detected easily in the late stages[13] along with recurrent seizures[15]. In the middle stages of globoid cell leukodystrophy, epileptic seizures and hypsarrhythmia-like patterns may be present[13, 16, 17]. In Zellweger Syndrome and

Table 1: Patient and EEG characteristics.

Number	Sex	Age (year)	Seizure onset (year)	Seizure type	Neurological impairment	Age on EEG	Background activity	Activation by			Epileptogenic focus	Secondary generalisation	Sleep spindles	K-complex
								HV	IPS	EC				
1	F	5.5	3	PM → SGTC	Moderate	9 months	Normal							
						3 years	Beta (right frontal)	–	–	–	–	–	+	+
						4.5 years	Beta (bifrontal)	–	–	–	Left F/C/T	+	Left ↓	+
						5.5 years	Beta (bifrontal)	–	–	–	Left F/T Right T in sleep ↑	+	Left ↓	+
2	M	12	4	GTC	Moderate	2.5 years	Normal							
						7 years	Normal	+	–	+	Right O/P/T Left P/T/F	+	–	
						9 years	Normal	+	+	+	Right O/P/T Left P/T/F	+	Scarce	Scarce
						11 years	Beta (fronto-central)	+	+	+	Right O/P/T Left P/T/F Right ↓ left ↑ in sleep	+	Scarce	Scarce
3	M	5	2.5	PM → SGTC	Moderate	9 months	Normal							
						2 years	Normal							
						4.5 years	Normal							
4	M	6.5	3	PM → SGTC	Severe	6.5 years	Beta (bitemporal)	NA	–	–	Left T/P Right T in sleep ↑	–	–	+
5	M	10	2.5	PM → SGTC	Severe	7 years	Normal	NA	+	+	Left T/P Right T in sleep ↑	+	+	+
6	F	12	4	GTC	Severe	9 years	Beta (bifrontal)	+	+	+	Right T Left T/F	+	Scarce	+
7	F	2	NA	NA	Mild	16 months	Normal							
8	F	2	NA	NA	Mild	18 months	Normal							
9	M	2	NA	NA	Mild	7.5 months	Normal							

Abbreviations: F, frontal; C, central; T, temporal; P, parietal; O, occipital; NA, not applicable; PM, partial motor seizure; GTC, generalised tonic–clonic seizure; SGTC, secondarily generalised tonic–clonic seizure; ↓, decreased; ↑, increased; HV, hyperventilation; EC, eye closure, IPS, intermittent photic stimulation.

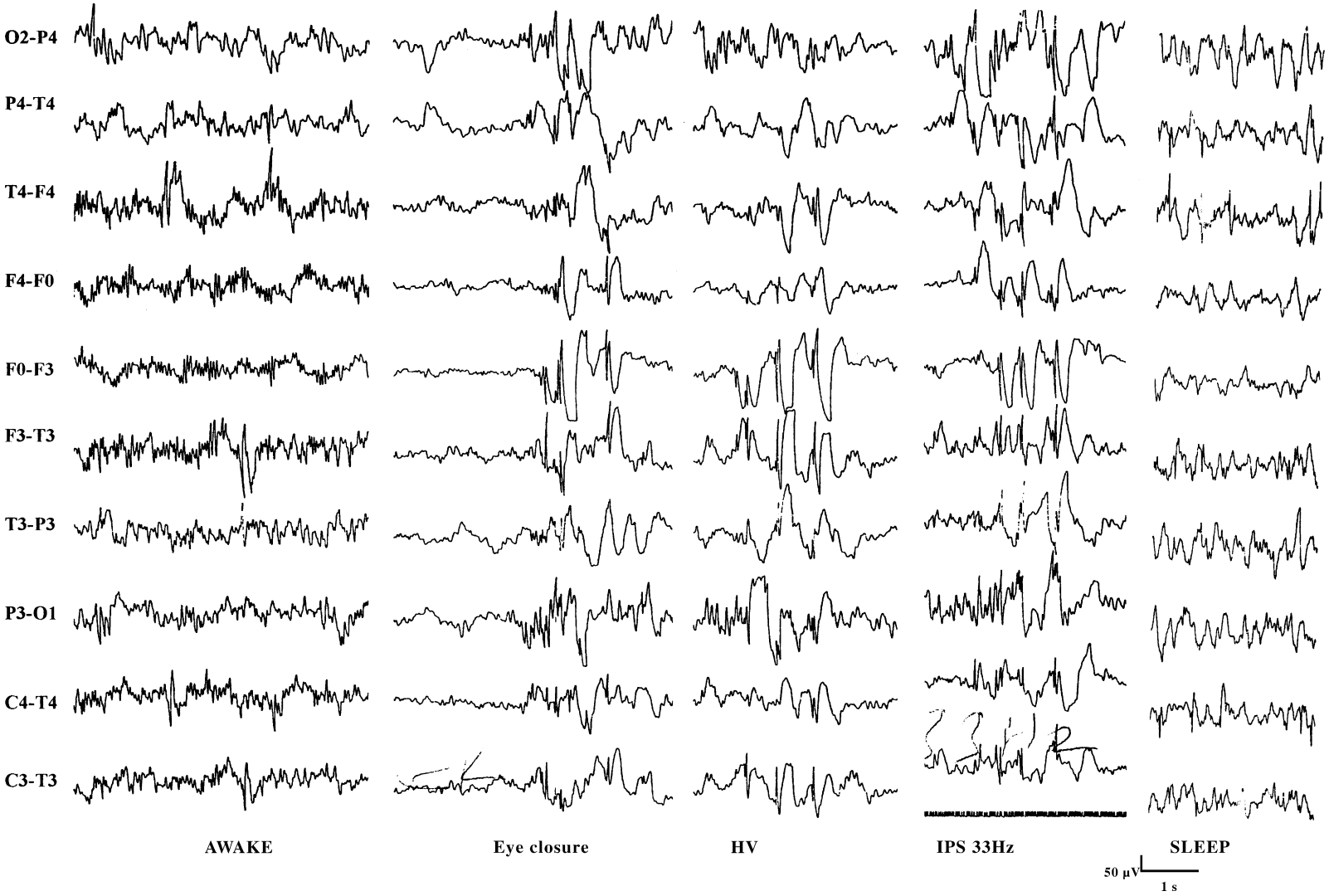
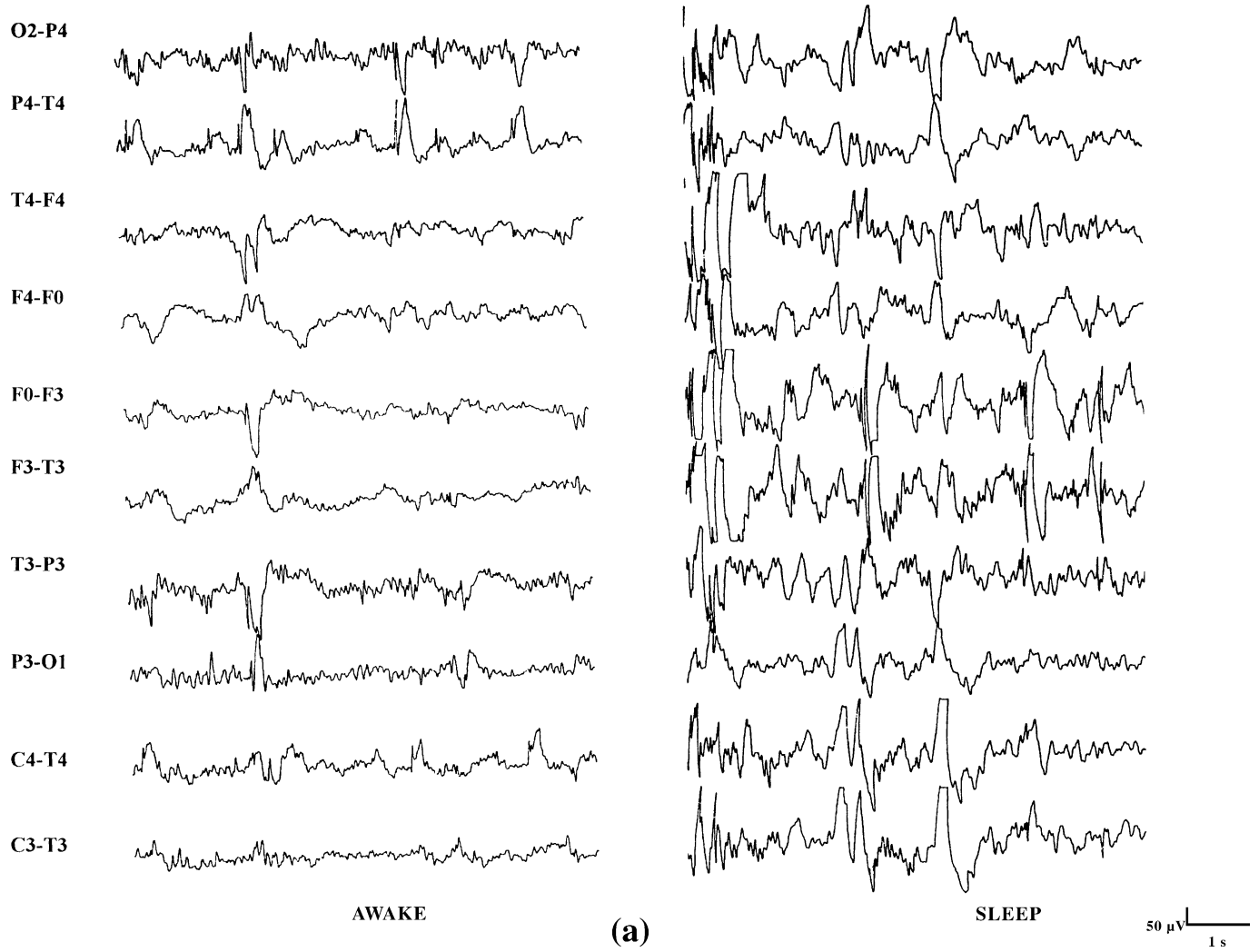


Fig. 2: Awake and asleep EEG of Patient 6 showing bilateral fronto-temporal beta activity and predominant right temporal foci and activation of spike-and-wave paroxysms with eye closure, HV and IPS.



(a)

Fig. 3: (*a*) The awake EEG of Patient 2 showing right occipito-parietal focal abnormality, a left frontal focus is more visible in sleep; (*b*) spike-and-wave paroxysms during IPS at 12 and 21 Hz.

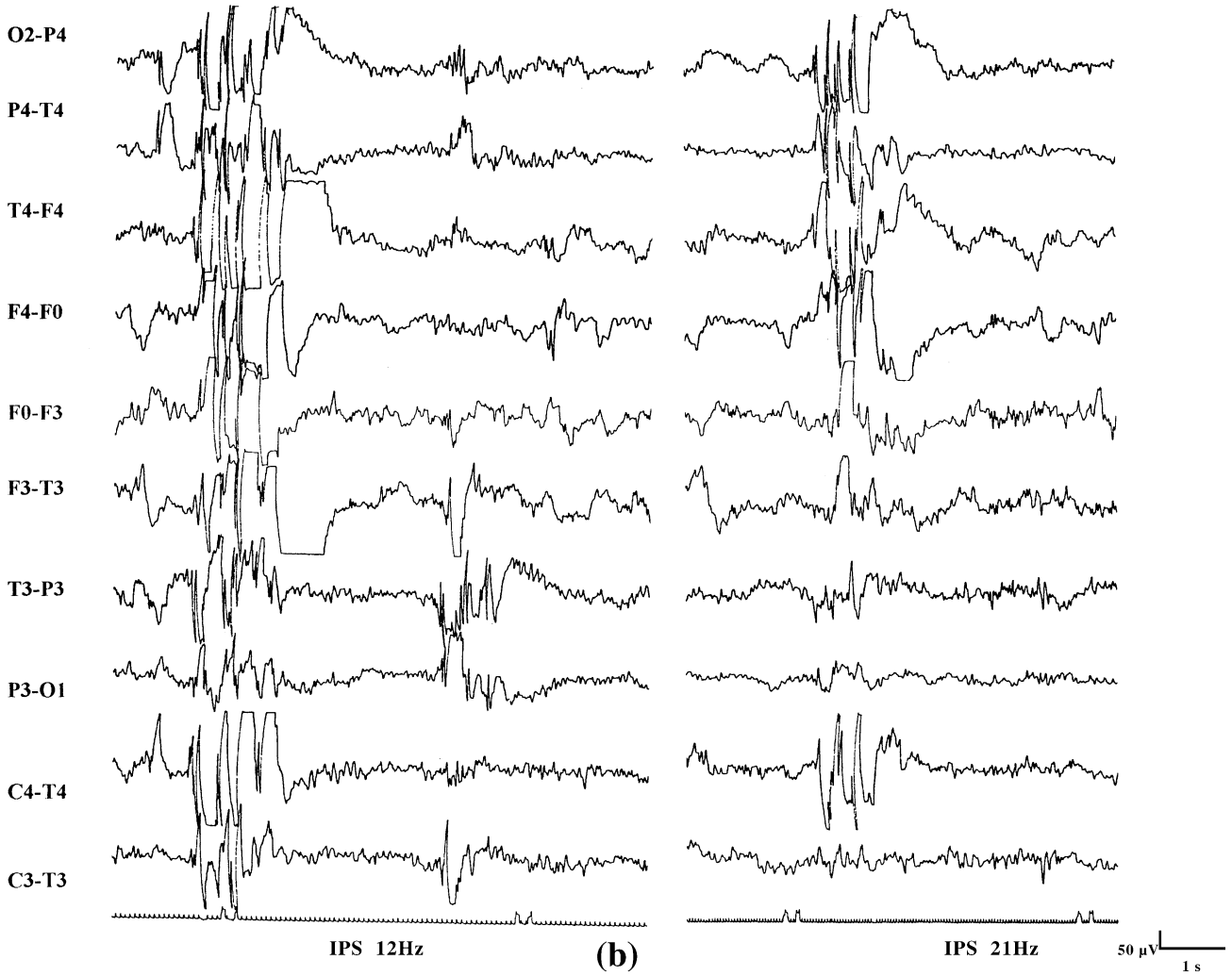


Fig. 3: (*Continued*).

Table 2: Seizure types of the published cases.

Year of publication	First author (reference #)	Number of patients	Patients with seizures	Age of seizure onset (year)	EEG abnormality	Reported seizure types
1990	Harbord [22]	2	2	2.5	+	GTC, atonic
1995	Van der Knaap [2]	8	6	1.5–12	4/6+	GTC
1996	Goutieres [20]	5	3	3–6	+	PM, GTC
1996	Singhal [5]	30	22	NS	10/22+	GTC
1997	Mejaski-Bosnjak [25, 26]	2	1	3	+	PM, GTC
1998	Topçu [7]	12	4	NS	+	GTC, myoclonic
1998	Koeda [27]	1	1	7	+	GTC
1999	Thelle [28]	2	1	6	+	PM → SGTC
1999	Yakinci [9]	1	1	2		GTC
1999	Takanashi [6]	1	1	5	+	GTC
2000	Biancheri [29]	1	0			
2000	Higuchi [23]	1	1	14	+	CPS
2001	Ben-Zeev [24]	12	6	NS	5/6+	GTC
2001	De Stefano [21]	2	2	1.5–7	+	CPS, GTC
2001	Yalçinkaya (current)	9	6	2.5–4	5/6+	PM → SGTC, GTC

Abbreviations: GTC, generalised tonic–clonic seizure; SGTC, secondarily generalised tonic–clonic seizure; CPS, complex partial seizure; PM, partial motor; NS, not specified.

neonatal adrenoleukodystrophy, refractory infantile spasms and tonic seizures starting from the onset have been reported[18]. In adrenoleukodystrophy, seizures and paroxysmal discharges develop occasionally a few years after the onset of the symptoms[13]. High-voltage polymorphic delta activity, especially over the temporo-occipital areas may be observed in adrenoleukodystrophy[17]. Whereas seizures are rare in the classical form of Pelizaeus–Merzbacher disease, intractable epilepsy is reported in the connatal form of this condition[13]. In Canavan and Alexander diseases, the EEG is often unremarkable, despite the presence of seizures and severe neurological involvement[17, 19].

To our knowledge, 80 patients with MLC have been reported in the literature and 51 (63.7%) of them had seizures (Table 2). The high incidence of epilepsy seems to be a particular feature of this recently described leukoencephalopathy[20]. The seizures are mostly generalised tonic–clonic, and sometimes partial with secondary generalisation. Myoclonic, atonic and complex partial seizures have been reported in a few patients[7, 21–23]. In our series, partial seizures with secondary generalisation were more common than generalised tonic–clonic seizures (four and two patients, respectively). Interestingly, minor head trauma was a precipitating factor for seizures in our patients. Trauma has been recognised as a trigger in 10–40% of the previously reported cases[5, 24]. The recurrence of seizures in MLC patients is not common. The literature reveals that the onset of convulsions varies between 1.5 and 14 years. However, in these cases the seizure frequency and the rate of disease progression have not been consistently reported. In some cases, patients responded quite well to antiepileptic drugs (AEDs). Although our cases generally responded to AEDs, two of the nine cases had refractory seizures with marked motor regression. It was noted that most epileptic cases had various EEG anomalies, however, as in one of our cases, EEG anomalies were not noted in two of Van der Knaap's cases, two of Singhal's and one of Ben Zeev's[5, 8, 24]. The motor development and neurological condition were better in our patients without epilepsy and with normal EEGs. The EEG abnormalities were spike or polyspike foci in the parietal, temporal and frontal areas with migratory changes in waking and sleep. Generalisation of the spike-and-wave paroxysms was seen during sleep, upon eye closure, during HV and IPS along with the increasing age of the patients. In some MLC patients, we observed activation of epileptogenic discharges by IPS after 7 years of age although their seizures began earlier. Two of our three patients with photosensitivity had refractory seizures with marked motor regression. Topçu *et al.*[1] observed good clinical outcomes in their patients with photosensitivity. Some of our patients had other background abnormalities, including focal or diffuse beta and theta activities.

In conclusion, it was noted that epilepsy was a frequent finding in children with MLC and usually emerged in early childhood age. While investigating these patients in childhood, epilepsy must be anticipated.

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