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Longitudinal EEG Studies in a Kindred with Lafora Disease

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Summary: We reviewed 18 EEG studies in four members of a family with the Lafora form of progressive myoclonic epilepsy. Each patient was the product of a consanguinous marriage and presented as a teenager with progressive seizures, myoclonus, dementia, and ataxia, and had biopsy proven disease. The EEG early in Lafora disease has spike–wave activity resembling that seen in a primary generalized epilepsy; the background slowing is more typical of a secondary generalized epilepsy. With disease progression, there is increased epileptiform activity, and a striking change in the spike–wave complexes, with a marked increase in frequency up to 6–12 Hz, and many more short duration polyspike components. Unlike some other forms of secondarily generalized epilepsy, the EEG in Lafora disease is distinguished by an increased frequency of the spike–wave complexes with disease progression. **Key Words:** Lafora disease—Seizures—Electroencephalography—Genetics.

Lafora disease (LD) is a form of progressive myoclonic epilepsy, characterized by seizures, myoclonus, dementia, and ataxia, with onset in adolescence and progression to death within several years (Van Heycop Ten Ham, 1968; Schwarz, 1977). Most descriptions of the electroencephalogram (EEG) in LD have been isolated case reports. One series (Tassinari et al., 1978) found early EEG changes similar to those in primary generalized epilepsy, but with progression the development of background slowing, polyspikes, and diffuse and multifocal spikes. We report the longitudinal EEG findings in four members of a kindred with LD. These patients had significant EEG findings that made discrimination from a primary epilepsy possible in the early stage of illness. With progression, all developed fast-frequency spike–waves of 10 Hz or greater, an unusual feature that may be quite distinctive in this disorder.

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MATERIALS AND METHODS

All four children were products of consanguinous marriages; two were brother and sister, and the others were first cousins. Each had the typical clinical features and progressive course of LD, with diagnosis confirmed by a skin or brain biopsy. Follow-up has been from 2.5 to 9 years; three patients have died. The principal clinical features are summarized in Table 1. Two illustrative case histories follow.

Patient #1

An isolated generalized tonic–clonic seizure occurred at age 12 years in this girl with normal birth and developmental history. In the following year, she developed severe behavioral problems, dysarthria, and ataxia, as well as poorly controlled absence, myoclonic, and tonic–clonic seizures. She became bedridden 4 years after onset. A corpus callosotomy temporarily decreased the seizure frequency; the diagnosis of LD was made at that time by a brain biopsy. The patient died 8 years after onset from multiple episodes of aspiration pneumonia.

Patient #4

At age 14 years, this girl developed myoclonic jerks of the extremities, but was still doing well in school. Birth and developmental history were normal. A brother had LD. Treatment with valproate

TABLE 1. *Clinical features in kindred with Lafora disease*

Patient number	Sex	Age at onset (years)	Presenting symptoms	Seizure type	Years followed	Number of electroencephalograms
1[a]	F	12	Seizure	Tonic–clonic, myoclonic, absence	8	7
2[a]	F	15	Myoclonus	Myoclonic, tonic–clonic, absence	9	2
3[a]	M	15	Seizure	Tonic–clonic, myoclonic	5	7
4	F	14	Myoclonus	Myoclonic, tonic–clonic	2.5	2

[a] Deceased.

resulted in initial improvement. Over several months, school performance deteriorated and generalized tonic–clonic seizures developed. Ataxia, dementia, and myoclonus have progressed but she is still ambulatory 2.5 years after onset.

Each patient had an initial EEG within 1 year of symptom onset and at least one subsequent EEG. A total of 18 studies were performed (range of two to seven) using the International 10–20 system of electrode placement on 8- to 21-channel instruments, with hyperventilation and photic stimulation performed routinely. All were obtained in the waking and drowsy states. Each was reviewed for background frequency and reactivity; the morphology, location, and frequency of the spike–wave activity; response to activating procedures; and the presence of independent focal spikes especially in the occipital regions. EEGs were separated according to stage of illness defined as early (<1 year from onset), intermediate (1–3 years from onset), or late (>3 years from onset).

RESULTS

The EEG features are summarized in Table 2. In the early stage (Fig. 1), there was mild slowing of the background activity that was reactive to eye opening in only one case. Trains of irregular, bilaterally synchronous 3 Hz spike–wave activity were seen at times diffusely, and at other times with an anterior or posterior emphasis. Two patients had EEGs performed in the intermediate stage. Both had increased background slowing (Fig. 2) and in one the frequency of the spike–waves had increased. In the late stage (Fig. 3), there was severe background slowing and a marked increase in the amount of epileptiform activity. In all cases, this consisted predominantly of 6–12 Hz spike–waves and short duration polyspikes, generally synchronous, with a diffuse or posterior emphasis. All patients had both synchronous and asynchronous epileptiform activity in the occipital areas. We were unable to reliably discriminate independent occipital spikes from fragments of the generalized discharges.

A photoparoxysmal response was seen inconsistently in three patients, although one had a brief generalized myoclonic seizure induced by photic stimulation. Hyperventilation was rarely activating. Myoclonus was also seen, frequently with no electrographic accompaniment.

TABLE 2. *Electroencephalographic features in Lafora disease*

Patient number	Stage of illness	Background		Spike–wave activity			Activation	
		Predominant frequency	Reactivity	Morphology	Location	Predominant frequency	Hv	Photic
1	Early	7	–	Single S–W	Diffuse	3	+	+
	Intermediate	4	–	Single S–W	Posterior	3	–	–
	Late	2–3	–	Single and poly S–W	Posterior	8–10	ND	–
2	Early	4–7	–	Single S–W	Posterior	3	–	–
	Late	3–5	–	Single and poly S–W	Posterior	6–8	ND	+
3	Early	4	–	Single S–W	Diffuse	3	–	–
	Late	2–3	–	Single and poly S–W	Diffuse	8–10	ND	–
4	Early	6	+	Single S–W	Anterior	3	–	+
	Intermediate	4	+	Single and poly S–W	Diffuse	10	–	–

ND, not done; Hv, hyperventilation; S–W, spike–wave; Hz, Hertz.

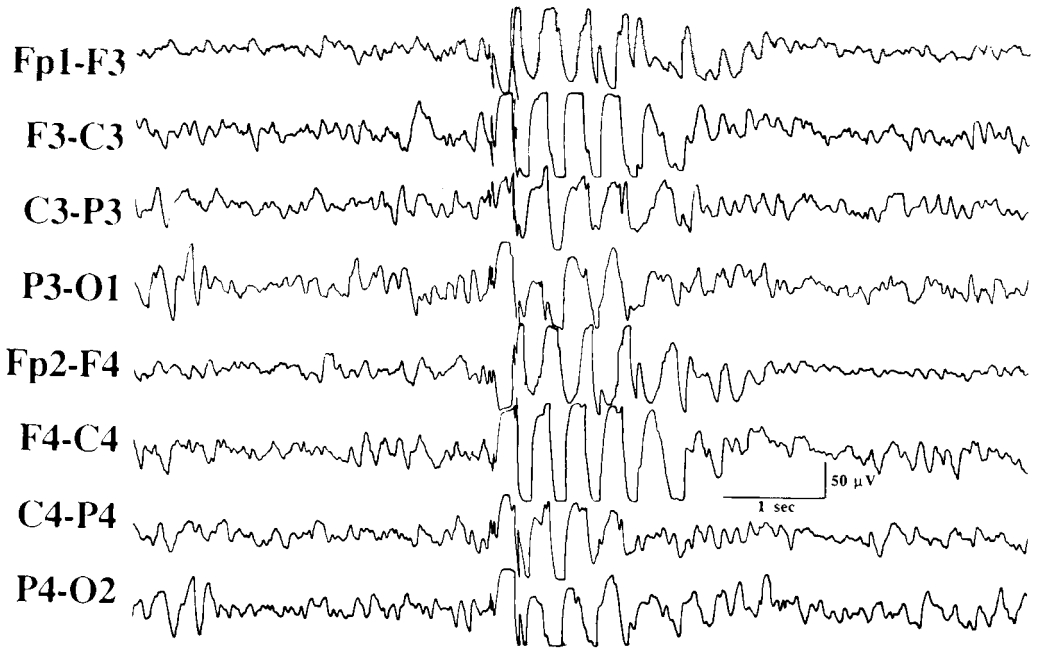

FIG. 1. Patient #1. Early stage, age 12 years, 1 week after first seizure. Electroencephalogram shows mild background slowing and trains of 3 Hz irregular spike–wave activity.

DISCUSSION

The progressive myoclonic epilepsies constitute one subtype of patients with secondary generalized epilepsy (Berkovic et al., 1986), and are a heterogenous group that can be distinguished by clinical features, biopsy findings, and in some patients by particular EEG characteristics. In some early case reports of LD (Van Heycop Ten Ham and De Jager, 1963; Janeway et al., 1967), the EEG pattern was thought to be nonspecific and nonprogressive, with background slowing and both diffuse and focal epileptiform activity. In a later series, Tassinari et al (1978) described an early stage (first year) of LD with EEG features similar to those seen in primary generalized epilepsy, with normal background activity and in four of six cases 3–5 Hz polyspike-and-wave activity anteriorly. None of our cases demonstrated a normal background, although all had an EEG within 1 year of onset; patient 1 was evaluated within a week of first seizure, with no medication, and the EEG already had mild slowing. Progressive

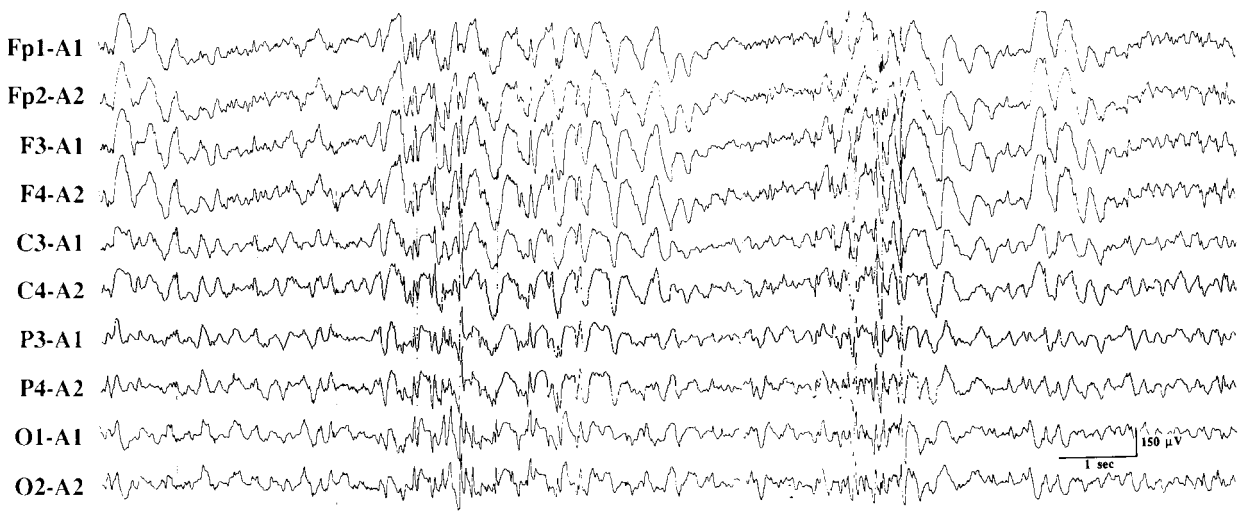

FIG. 2. Patient #4. Intermediate stage, age 16 years, 2 years after onset. Electroencephalogram shows remnants of 3 Hz spike–waves, with faster frequency spike–waves up to 12 Hz.

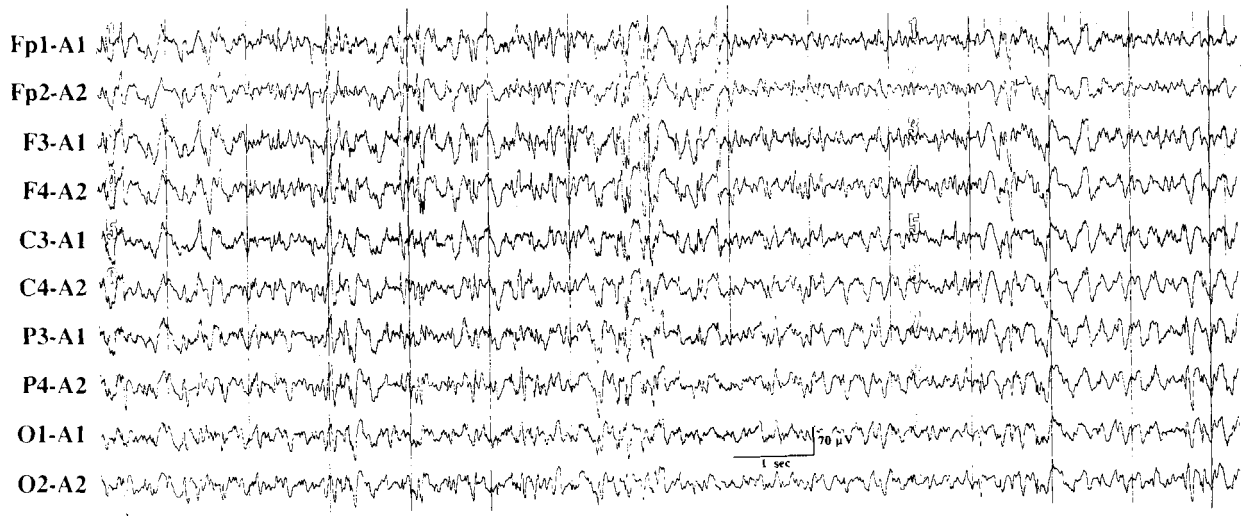

FIG. 3. Patient #3. Late stage, 4 years after onset. Electroencephalogram shows slow background with overlying beta activity, fast spike–waves and polyspikes.

background slowing coinciding with disease progression and seen in each of these cases has been described by others (Tassinari et al., 1978; Kobayashi et al., 1990). Intermixed faster frequencies have been previously noted (Van Heycop Ten Ham and De Jager, 1963; Roger et al., 1967). We believe that this is most probably due to the presence of frequent intermixed low-amplitude fast spike–wave complexes, and drug-induced beta activity as all our patients were receiving barbiturates or benzodiazepines.

The trains of 3 Hz spike–wave activity seen in the early EEGs in this family were slightly irregular with an anterior emphasis in just one case; hyperventilation was rarely activating. Overall, while the spike–wave activity was close to that seen in primary generalized epilepsies, the background slowing made this diagnosis unlikely. Periodic recurrence of the epileptiform activity has also been seen (Riehl et al., 1967; Mancardi et al., 1979), but was not present in our cases. With disease progression, polyspikes (Roger et al., 1967), 2–3 Hz spike–waves (Saenz Lope et al., 1974), and 3–5 Hz spike–waves (Tassinari et al., 1978) have been described. The prominent EEG feature with disease progression in these cases was 6–12 Hz spike–wave activity. Tassinari et al. (1978) briefly mentions fast spike–waves, and they are present in some illustrations in the publications of Janeway et al. (1967) and Kobayashi et al. (1990), but these unusual discharges have not been emphasized as a feature of this disorder. The consistent photoparoxysmal response noted by others (Tassinari et al., 1978) was inconsistently seen in these cases.

Occipital spikes have been described as a characteristic feature of LD (Tassinari et al., 1978), and many patients including ours described episodic visual phenomena consistent with occipital seizures. Independent occipital seizures provoked by photic stimulation have been recorded in two patients (Tinuper et al., 1983,1985). We could not distinguish independent occipital spikes with certainty as they resembled fragments of the more generalized discharges.

Some other forms of secondary generalized epilepsy also show progressive EEG changes over time. A late-onset form of Lennox–Gastaut syndrome has been described (Drury and Dreifuss, 1987) where at onset in adolescence the EEG shows normal background and 3–5 Hz spike–wave activity, and over 20 years mild background slowing and slow spike–wave activity develop. Baltic myoclonus, another progressive myoclonic epilepsy, may have an initial clinical presentation similar to LD: 3–5 Hz spike–waves with an anterior emphasis, progressive background slowing, and slowing of the spike–waves have been described (Koskiniemi et al., 1974). To our knowledge, no form of secondary generalized epilepsy has previously been associated with the development of faster spike–waves as the predominant epileptiform activity with disease progression.

Although the EEG findings we report may be specific to this kindred, the cases are typical of LD in their clinical features. The changes appear to be quite distinctive. Even at onset the background slowing should suggest that a diagnosis other than an idiopathic generalized epilepsy be considered,

and the progression to prominent fast spike–wave complexes over time appears to be unique.

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RÉSUMÉ

Les auteurs ont revu 18 enregistrements EEG pratiqués chez 4 membres d'une famille présentant une maladie de Lafora. Chaque patient était issu d'un mariage consanguin et a présenté dans l'adolescence l'association progressive de crises, d'un myoclonus, d'une démence et d'une ataxie; le diagnostic de la maladie a été confirmé par une biopsie. L'EEG présente, à la phase initiale de la maladie de Lafora, un aspect comparable à celui de l'épilepsie généralisée idiopathique, mais le ralentissement de l'activité de fond évoque davantage l'EEG des épilepsies généralisées symptomatiques (EGS). Pendant la progression de la maladie, les auteurs ont constaté une augmentation de l'activité épileptique EEG, avec modification importante de la morphologie des PO, qui ont augmenté de fréquence, jusqu'à 6–12 c/s, avec composantes accrues en Polypointes rapides. Contrairement à d'autres formes d'EGS, l'EEG de la maladie de Lafora se distingue par une augmentation de fréquence des PO au cours de l'évolution.

(P. Genton, *Marseille*)

RESUMEN

Se revisan 18 estudios de EEG en 4 miembros de una familia con la forma de Lafora de una epilepsía mioclónica progresiva. Cada paciente fue producto de un matrimonio consanguíneo y en su adolescencia presentaron ataques progresivos, mioclonías, demencia y ataxia, y se les practicó una biopsia que confirmó la enfermedad. Los EEGs practicados precozmente en la enfermedad de Lafora tienen una actividad de punta-onda que semeja la que se observa en epilepsía generalizada primaria y la lentificación de la actividad de fondo es más típica de epilepsía generalizada sencundaria. A medida que la enfermedad progresa se observó un incremento de la actividad epileptiforme y un cambio sorprendente en los complejos punta-onda con marcado incremento de la frecuencia hasta 6–12 Hz. y muchos más componentes de polipuntas de breve duración. Contrariamente a otras formas de epilepsía generalizada secundaria el EEG en la enfermedad de Lafora se caracteriza por un incremento de la frecuencia de los complejos punta-onda a medida que la enfermedad progresa.

(A. Portera-Sánchez, *Madrid*)

ZUSAMMENFASSUNG

Wir beurteilten 18 EEG-Untersuchungen bei 4 Mitgliedern einer Familie mit der Lafora-Form der progressiven Myoklonus-Epilepsie. Jeder Patient entstammte einer konsanguinen Ehe und wurde als Teenager mit progressiven Anfällen, Myoklonus, Demenz und Ataxie auffällig; die Diagnose wurde durch Biopsie bestätigt. Das EEG im frühen Verlauf einer Lafora-Erkrankung zeigt Spike Wave Aktivität, die der bei primär generalisierter Epilepsie ähnelt, während die Hintergrundaktivität mehr für eine sekundär generaliserte Epilepsie typisch ist. Mit fortschreitender Erkrankung tritt vermehrt epileptische Aktivität und ein deutlicher Wechsel der Spike Wave Komplexe mit starkem Ansteigen der Frequenz auf 6–12 Hz und vermehrten kurzdauernden Polyspike-Komponenten auf. Im Gegensatz zu anderen Formen sekundär generalisierter Epilepsien zeigt das EEG bei der Lafora-Erkrankung mit Erkrankungsfortgang eine zunehmende Frequenz der Spike Wave Komplexe.

(C. K. Benninger, *Heidelberg*)