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EXPERIMENTAL / LABORATORY STUDIES

Lafora Body Disease: Clinical, Electrophysiological and Histopathological Findings

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Lafora body disease (LD) is inherited by autosomal recessively. Clinical findings usually start between 6 and 19 years of age, and the disease has its peak around 15 years of age. Clinical findings often begin at the end of the first decade or at the beginning of the second decade with the appearance of epileptic seizures. Seizures are myoclonic, generalized tonic-clonic, or focal occipital types. Seizures are followed by a decline in the intellectual functions and severe motor and coordination dysfunction. Diagnosis is made by polyglucosan inclusions (Lafora bodies) shown in biopsies of the skin, striated muscle, liver, brain, and/or bone (1).

In this article, 2 patients who were admitted by the complaints of progressive generalized myoclonic seizures, and who were diagnosed by LD after investigation of the etiological factors causing this clinical picture, are presented along with their clinical, laboratory and histopathological features.

Case 1

A 34-year-old male was admitted to the Emergency Room with epileptic status. Prenatal, natal and postnatal periods, and developmental milestones were normal. His parents noticed that he had myoclonic jerks, personality changes and development of exaggerated nervousness, and was performing poorly at school at the age of 16. They also stated that he was unable to complete his education. Later, he developed incoordination of movements. In the previous 2 years, he could manage his daily activities with support, and became bedridden. Generalized tonic-clonic seizures were added to the clinical picture 2 years after the myoclonic jerks. He was still taking Na-Valproate (1000 mg/d) and phenobarbital (200 mg/d) but his seizures were not completely under the control. For the previous 2 days, he had not been taken the antiepileptic drugs regularly and the frequency and severity of the seizures had been increased.

His physical examination was normal. In his neurological examination apathy associated with predominant cognitive impairment was determined. Cranial nerves and brainstem reflexes were normal. Muscle power was normal. There was ataxia in the trunk and limbs and also intentional tremor. Deep tendon reflexes were hypoactive and Babinski's sign was bilaterally indifferent.

Laboratory

Complete blood cell count, blood biochemistry including electrolytes and liver and renal function tests were normal. Thyroid function tests and the other hormone profile, lactic and pyruvic acid, collagen tissue tests, immunoglobulins of serum and cerebrospinal fluid (CSF) and serological tests for infectious agents in both

serum and CSF were normal. Electroencephalography (EEG) showed diffuse background irregularity consisting of slow activities and subcortical active epileptic activity. Cerebral magnetic resonance imaging (MRI) was normal. The biopsy obtained from the biceps turned out to be normal. Light microscopic examination of the axillary skin biopsy by Periodic acid schiff (PAS) and Hemotoxylin-eosin revealed multiple Lafora bodies in the ductal epithelial cytoplasms of the sweat glands (Figures 1,2).

Treatment and Prognosis: The patient, whose seizures could not be controlled by thiopentone sodium infusion (100 cc/h), underwent general anesthesia and his seizures were partially controlled. The antiepileptic drugs, Na-Valproate (1500 mg/d), clonazepam (3 mg/d), and lamotrigine (150 mg/d) were continued. In the follow-up, he had status epilepticus again and died in the Intensive Care Unit.

Case 2

A 15-year-old female was admitted to our department with the complaint of frequent seizures. Prenatal, natal and postnatal periods, and developmental milestones were normal. Her parents noted that she had been put on Na-Valproate (400 mg/d) due to generalized tonic-clonic seizures, which occurred during sleep, at the age of 9 years. Carbamazepine and vigabatrine were added to the treatment because her seizures could not be controlled. They mentioned that myoclonic jerks had begun approximately 30 months after the generalized seizures. Later, the complaints of personality changes, decline in performance at school, speech disturbance, and incoordination of movements were added. She had been bedridden for the previous year. She had been diagnosed with subacute sclerozing panencephalitis in another medical center and was still taking vigabatrine (2500

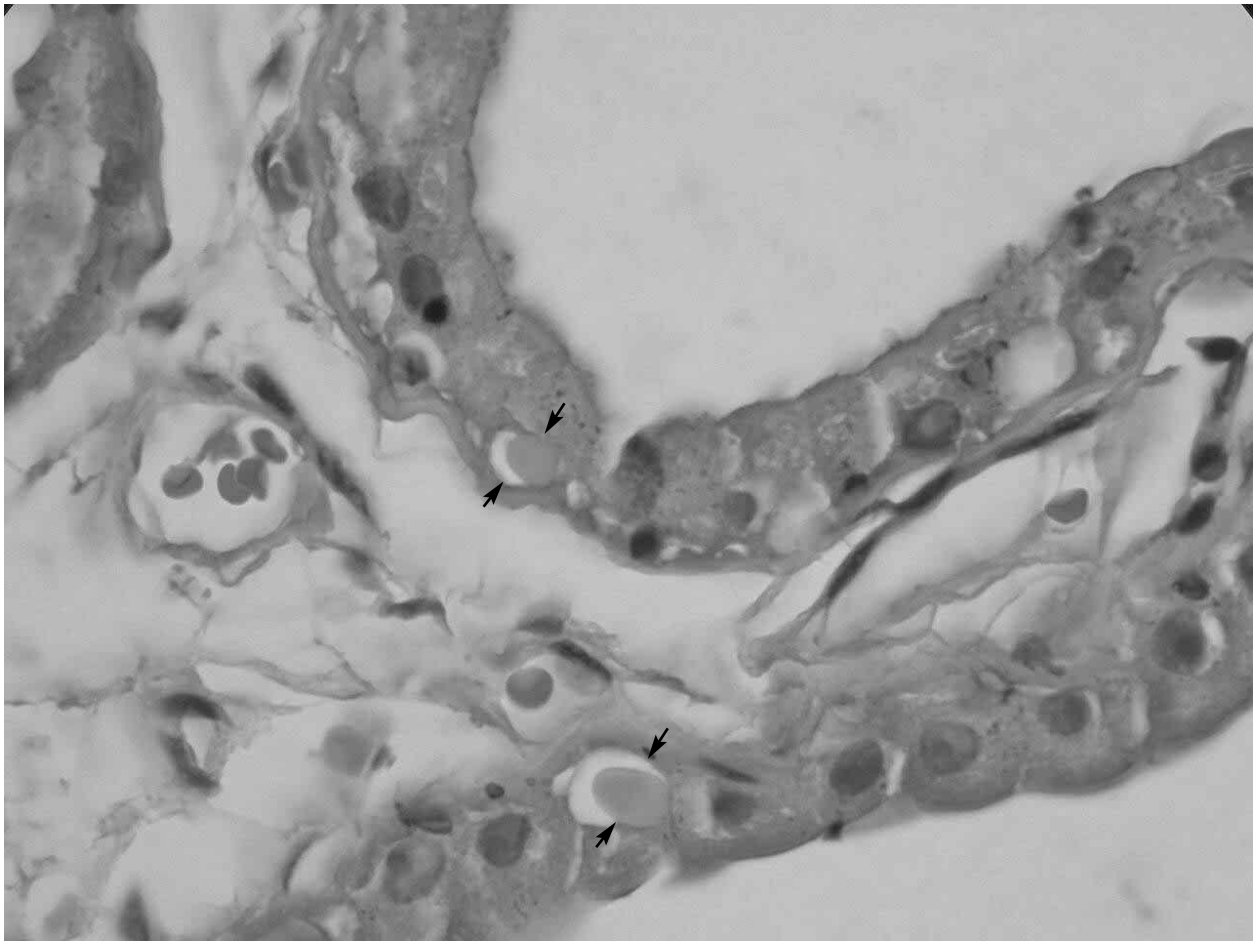

Figure 1. Lafora bodies in the ductal epithelial cytoplasms of the sweat glands by Hemotoxylin –Eosin (HE x 1000).

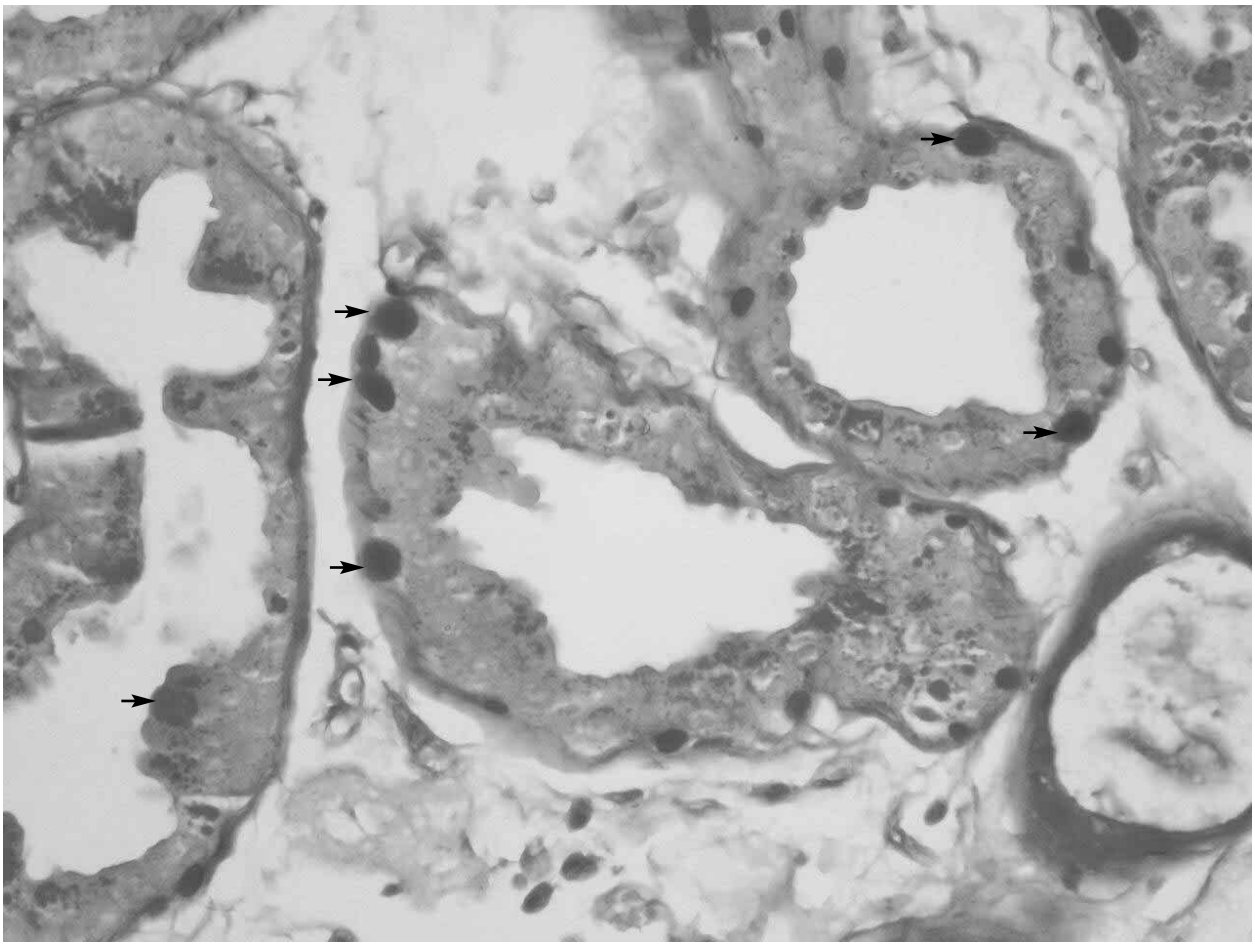

Figure 2. Lafora bodies in light microscopic examination of the axillary skin biopsy by Periodic Acid Schiff (PAS x 400).

mg/d), lamotrigine (150 mg/d), and clonazepam (50 mg/d) in addition to inosiplex.

Her physical examination was normal. In her neurological examination, she was mentally retarded, and she had apathy associated with predominant cognitive impairment. Cranial nerves and brainstem reflexes were normal. Muscle power was normal. There was ataxia in the trunk and limbs and intentional tremor. Deep tendon reflexes were hyperactive. Babinski's sign was bilaterally indifferent. Hoffman's and Tromner's sign were bilaterally positive. During the neurological examination, myoclonic jerks localized in the left arm and around the mouth were observed by stimulation.

Laboratory

Complete blood cell count, blood biochemistry including electrolytes, and liver and renal function tests were normal. Thyroid function tests and the other hormone profile, lactic and pyruvic acids, collagen tissue tests, immunoglobulins of serum and cerebrospinal fluid (CSF), and serological tests for infectious agents in both serum and CSF were normal. EEG showed diffuse background irregularity consisting of slow activities and bursts of nonrhythmic slow activity. There were infarct areas localized to the subcortical white matter in the frontal and parietal regions in the cerebral MRI (Figure 3). The biopsy obtained from the biceps and superficial peroneal nerve were normal. Light microscopic examination of the axillary skin biopsy by PAS and Toluidine blue revealed multiple PAS-positive Lafora bodies in the ductal epithelial cytoplasms of the sweat glands.

Treatment and Prognosis: Diazepam infusion was started. Vigabatrin was stopped and Na-Valproate was added slowly. Lamotrigine (150 mg/d), Na-Valproate

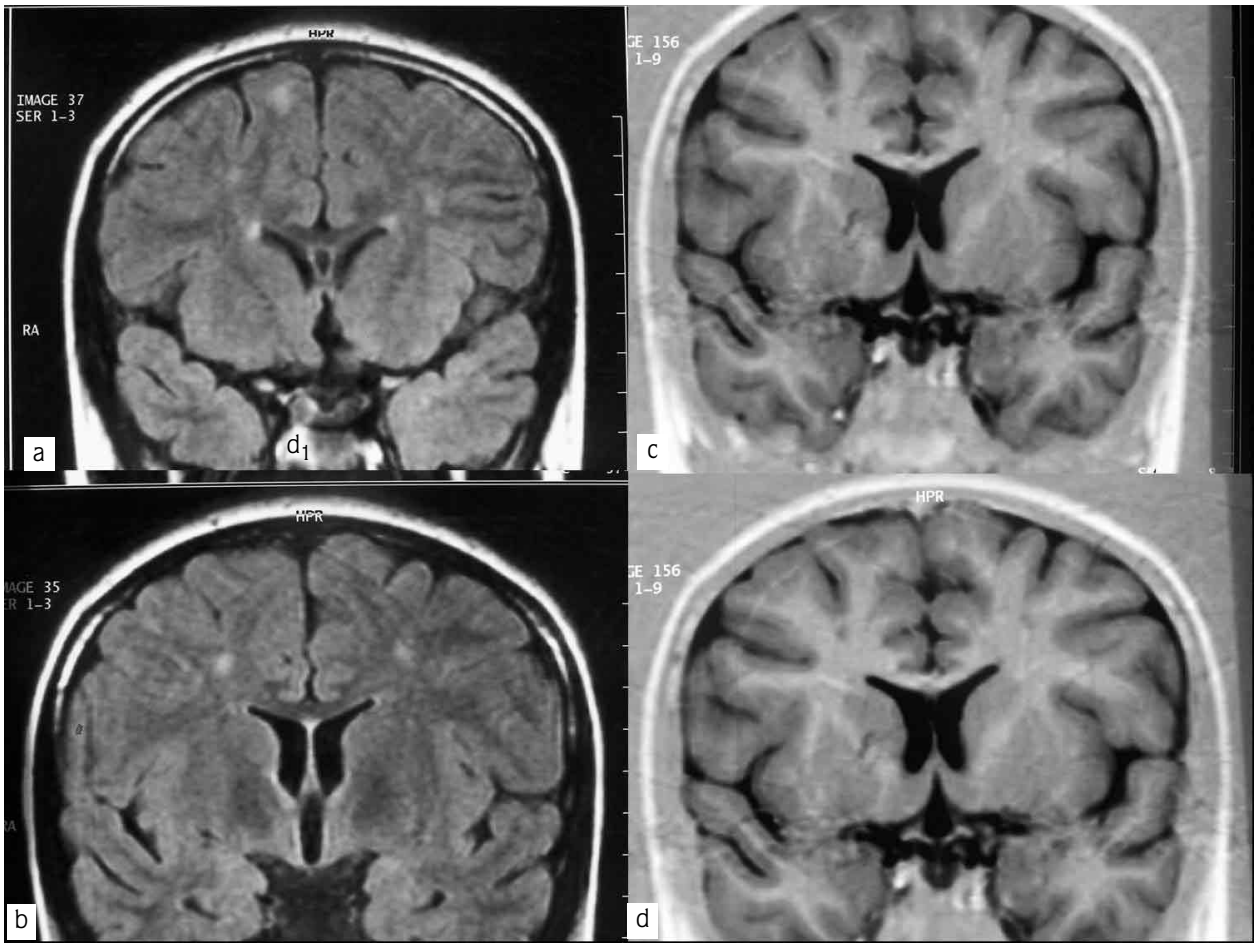

Figure 3. Multiple infarct areas are seen in the frontal and parietal subcortical white matter on coronal Flair (a,b) and Tirm (c,d) MRI.

(1500 mg/d), and clonazepam (4 mg/d) were continued. She was completely seizure-free for almost 2 months and the severity and frequency of the myoclonic jerks decreased predominantly.

Genetically inherited progressive myoclonic epilepsies (PMEs) are clinically characterized by stimulus-sensitive myoklonus, generalized tonic-clonic, and absence seizures associated with progressive neurological deterioration (dementia, ataxia, different focal neurological findings) (1). PMEs are very rare and heterogeneous diseases. They are often inherited autosomal recessively except for autosomal dominant dentatorubral-pallidolusian atrophy and mitochondrial encephalopathy associated with ragged red fibers (MERRF). LD is a hereditary progressive myoclonic epilepsy consisting of Unverricht-Lundborg diseas, Lafora body disease, neuronal ceroid lipofuscinosis, mitochondrial diseases, and sialidosis (2-4). This disease, which is inherited autosomal recessively, manifests in the late childhood or adolesan period. The onset is usually between 11 and 18 years of age, but patients with early onset and late onset have been reported (5-7). LD is caused by a mutation in the EPM2A gene, localized on the chromosome 6q24, which encodes 2 isoforms of the laforin protein thyrosin phosphatase, and this mutation is shown in 80% of the patients (8-10). It is frequently seen in India, Pakistan, North Africa, the Middle East, and other countries in which consanguinous marriage often occurs (11).

The clinical findings, beginning with seizures, may be generalized tonic-clonic and/or myoclonic seizures. Occipital seizures characterized by photoconvulsive, visual hallucinations and scotoma might also be seen.

Progressive deterioration in the neurological picture, such as ataxia, dementia, psychosis, dysarthria, amaurosis, mutism, and muscle weakness, and respiratory failure are associated with the seizures and it causes death in patients between 17 and 30 years of age (3). Additionally, cardiac conduction defects have been reported (5).

In the differential diagnosis, the diseases mentioned above, which play a role in the etiologies of hereditary PMEs, should be ruled out. MERRF is characterized by CNS dysfunctions, such as myoclonic epilepsy, generalized tonic-clonic seizures, deafness, spasticity, myoclonus and dementia, and pigmentary retinopathy, cardiomyopathy, renal tubular dysfunction, peripheral neuropathy, and asymptomatic myopathy associated with RRFs (12,13). Univerricht-Lundborg disease is characterized by recurrent myoclonic and generalized tonic-clonic seizures. Myoklonus occurs 1 to 5 years after the other clinical findings. While the myoclonous is asynchronous, it is bilateral and evident in the proximal muscle groups. The clinical findings begin with convulsions between 6 and 13 years of age. Myoclonic seizures are severe and continuous, and are provokated by movement, stress and sensory stimuli. Mental impairment and dementia may develop. Cerebellar findings occur at the late phase of the disease, usually 10 to 20 years after the onset. EEG findings are typical (1,14). Neuronal ceroid lipofuscinosis is a lysosomal storage disease. It has 4 types: infantile, late infantile, juvenile, and adult. Most patients have neurological findings including ocular and cognitive/motor dysfunction, and seizures that can not be controlled (15). Sialidosis has 2 types. Late-onset type I is characterized by visual defekts, myoclonic syndrome, cherry-red macular syndrome, ataxia, and hyperreflexia. Early-onset type II presents with Hurler-like phenotype, mental retardation, hepatosplenomegaly, and disostosis multiplex.

In our cases, the clinical findings started between the ages of 9 and 16 with myoclonic and generalized tonic-clonic seizures consecutively, and this was associated with ataxia and mental involvement over time. All the above mentioned diseases were excluded by the absence of RRFs and fingerprint or curvilinear bodies in the muscle and nerve biopsy respectively, the absence of myoclonus predominantly in the proximal muscle groups, the occurence of ataxia and mental impairment in the early phase, and a normal fundoscopical examination.

LD is diagnosed by the determination of Lafora bodies in different tissues in addition to molecular biological studies. Skin biopsy is an easy and effective method. The axillary skin biopsy performed when LD is suspected along with clinical findings may help in the diagnosis before mental deterioration and dementia occur (16). In our cases, while the muscle biopsy was normal, PAS-positive Lafora bodies were shown in the axillary skin biopsy.

LD has an unfavorable prognosis, and patients usually die within 10 years of the clinical findings at onset.

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