LAFORA DISEASE AND CONGENITAL GENERALIZED LIPODYSTROPHY: A CASE REPORT

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We report a patient with congenital generalized lipodystrophy who had suffered from seizures, myoclonus, ataxia and cognitive decline since late childhood. Laforta disease was diagnosed based on skin biopsy results, which revealed pathognomonic Laforta bodies. The results of genetic analysis for mutations in EPM2A and EPM2B genes were negative. This is the first case report describing an association between congenital generalized lipodystrophy and Laforta disease. Further studies focusing on the relationship between these two diseases and the identification of a third locus for Laforta disease are needed.

Key Words: Laforta disease, lipodystrophy, myoclonus, progressive myoclonic epilepsy

Congenital generalized lipodystrophy (Berardinelli-Seip syndrome) was initially reported by Berardinelli [1] and Seip [2] and is an extremely rare autosomal recessive disorder with genetic heterogeneity. Its prevalence has been estimated to be less than one in one million. Three different loci (AGPAT2, BSCL2 and CAV1), which map to chromosomes 9q34, 11q13 and 7q31, respectively, have been identified [3–5]. The disease is characterized by a generalized lack of body fat and extreme muscularity from birth, acromegoloid features, hypertriglyceridemia, hepatomegaly and insulin resistance (manifested as acanthosis nigricans). The central nervous system is seldom affected, except for the presence of mental retardation in approximately 80% of individuals with mutations in BSCL2 [6]. Laforta disease (LD) is also an uncommon autosomal recessive disorder that presents with seizures, myoclonus and cognitive decline, which develop during late childhood or adolescence. We report a child with congenital generalized lipodystrophy and LD, a previously undescribed association, and attempt to clarify the relationship between these two diseases.

CASE PRESENTATION

An 11-year-old boy presented at our pediatric neurology division with a 2-year history of seizures, myoclonus, ataxia and cognitive decline. The patient was born uneventfully to unrelated Taiwanese parents. Generalized lipodystrophy with muscular hypertrophy, acromegoloid features, hepatomegaly, hirsutism, hypertrophic cardiomyopathy, hypertriglyceridemia (triglycerides, 6.9 mmol/L) and insulin resistance (insulin, 450.7 pmol/L and acanthosis nigricans) had been noted since infancy, and congenital generalized lipodystrophy was diagnosed clinically. He was prescribed diet modification (a low-fat diet) and received regular follow-up at our pediatric genetic division. The patient had psychomotor retardation; he started walking at 3 and talking at 4 years of age. The condition improved gradually after he received special
education, and he was able to ambulate freely and express himself in simple sentences. From the age of 9 years, dysarthria, decreased verbal output and ataxia were noted by his school teacher. Several months later, he experienced tonic-clonic seizures with fever. Electroencephalography (EEG) showed posteriorly dominant irregular spike-wave discharges (Figure 1). During the following 2 years, the patient developed erratic myoclonus, global developmental regression with loss of language and cognition, and became bedridden. Treatment with valproate and levetiracetam was initiated and he was hospitalized due to intractable seizures.

Neurological examination showed severe cognitive impairment, frequent small-amplitude myoclonus and few spontaneous movements. Diffuse fragmentary myoclonus was present at rest and was exaggerated by action and excitement. The cranial nerves were intact and deep tendon reflexes were slightly decreased. His head size, weight and height were normal for his age. A general physical examination was unremarkable except for the lipodystrophic, acromegaloïd features (including prognathism, prominent orbital ridges and enlarged hands and feet), acanthosis nigricans and hepatomegaly mentioned previously (Figure 2).

Examination of ocular fundi was normal. The results of routine hematological, biochemical and metabolic investigations, including lactate/pyruvate ratio, copper, ceruloplasmin, and cerebrospinal fluid examination were within normal limits. Brain magnetic resonance imaging scans showed mild generalized atrophy with ventriculomegaly. EEG showed diffuse slow background activity and absence of normal sleep rhythms and epileptiform activity. Visual evoked potentials showed increased bilateral P100 latency and auditory brainstem evoked potentials revealed bilateral poor wave responses at 90 dB click stimulation. Somatosensory evoked potentials were not investigated due to excessive myoclonus and difficulty with sedation. The results of genetic studies for spinocerebellar ataxias and dentatorubropallidoluysian atrophy were negative.

LD was suspected on the basis of the clinical findings. The diagnosis was confirmed following a skin biopsy obtained from the axilla, which revealed periodic acid-Schiff (PAS)-positive intracellular polyglucosan inclusion bodies in the eccrine sweat gland duct cells (Figure 3), the pathognomonic Lafora bodies. The results of further genetic studies using sequence...
analysis for mutations in *EPM2A* and *EPM2B* genes were negative. Clonazepam, nitrazepam and lorazepam were prescribed in addition to valproate and levetiracetam; chloral hydrate was also administered as required, since the continuous myoclonus only resolved during sleep. The patient’s myoclonus improved and the frequency of seizures was reduced under this drug regimen. The patient remained at home in a near-vegetative state, with tracheostomy and tube feeding.

**DISCUSSION**

The term progressive myoclonic epilepsy covers a large and varied group of diseases characterized by myoclonus, generalized tonic-clonic seizures, and progressive neurological deterioration, which is typically accompanied by cerebellar signs and dementia. LD, an autosomal recessive disorder, is referred to as progressive myoclonic epilepsy type 2, and its clinical and histopathological features were first described by Gonzalo Lafora, a Spanish neurologist, in 1911. LD occurs worldwide, though exact prevalence figures are not available. Although rare in the outbred populations of the United States, Canada, China, and Japan, LD is relatively common in the Mediterranean basin including in Spain, France, and Italy, as well as in restricted regions of central Asia, India, Pakistan, northern Africa, the Middle East and other parts of the world with a high rate of consanguinity [7]. To the best of our knowledge, there have been no documented cases in Taiwan. The characteristic clinical presentation of LD includes the onset of myoclonus, visual hallucinations or transient blindness (occipital seizures) and multiple seizure types in a previously normal child. The mean age of onset is 14 years, but ranges from 10 to 17 years [8]. Myoclonus and occipital seizures are cardinal components of LD [9]. In the years following onset, the symptoms of LD progress towards intractable action-sensitive and stimulus-sensitive myoclonus, refractory seizures, psychosis, ataxia, dysarthria, and dementia. Most patients die within 10 years of onset, usually from complications related to degeneration of the nervous system and status epilepticus [8].

The diagnosis of LD depends on the presence of pathognomonic Lafora bodies. These are PAS-positive intracellular inclusions consisting of an abnormal form of glycogen termed polyglucosan that accumulates in neurons and other tissues, such as the heart, liver, muscle, and skin sweat glands, though only the central nervous system is clinically affected. In the skin, Lafora bodies are found in eccrine gland duct cells and in apocrine myoepithelial cells, and a skin biopsy is the least invasive pathologic diagnostic method, with very high, though not perfect, sensitivity [10–13]. Interpretation of skin biopsy findings carries a risk of false-negative results, especially in newly symptomatic individuals, and a risk of false-positive results because of the difficulty in distinguishing Lafora bodies from normal PAS-positive polysaccharides in apocrine glands in axillary or genital biopsies [12,14]. The biopsy in our patient came from the axilla and revealed PAS-positive inclusions in the eccrine gland duct cells, which could be identified as unmistakable Lafora bodies. To confirm our diagnosis, we reviewed the related literature to identify any other conditions associated with similar inclusion bodies; similar PAS-positive inclusions occurred in the human brain, called corpora amyacea, and in hepatocytes due to medication effects in one case [15], but no such bodies were reported in the skin. Lafora bodies also resemble the polyglucosan bodies found in glycogen storage disease type IV and adult polyglucosan body disease, but the clinical presentations are different. Therefore, the specific skin pathology provides a reliable diagnosis of LD: PAS-positive inclusion bodies in a previously normal child between 6 and 18 years of age with myoclonic epilepsy are pathognomonic of LD [9].

LD is genetically heterogeneous with at least three loci, of which two are known, *EPM2A* and *EPM2B* (*NHLRC1*). *EPM2A* is a four-exon gene located on chromosome 6q24 encoding laforin, a dual-specificity phosphatase with a carbohydrate-binding domain. It could be involved in detecting the appearance of polyglucosans and initiating mechanisms to eliminate these compounds, or preventing their further formation [16]. *EPM2B* has a single large exon at 6p22, which encodes the malin E3 ubiquitin ligase working in the ubiquitin-proteasome system, the major nonlysosomal pathway for intracellular protein degradation [17]. The mechanism by which mutations in either *EPM2A* or *EPM2B* result in LD and the exact role of the Lafora bodies in the pathogenesis of LD requires further study. Accumulated evidence points to LD as primarily a disorder of cell death with impaired
clearance of misfolded proteins, though the mechanism of polyglucosan inclusion body accumulation remains unknown. Laforin and malin interact and their primary roles appear to be in protecting tissues from accumulating polyglucosans by regulating the proteins involved in glycogen metabolism [18–21]. Several studies are investigating the biochemical pathways that connect laforin and malin to polyglucosan synthesis or degradation [22].

More than 90% of LD patients can be shown to harbor mutations in EPM2A or EPM2B [23]. The remaining patients, such as our patient, may have mutations in noncoding regions or in a third, as yet unidentified, gene [24]. Laboratories offering genetic testing for LD currently use only sequencing, and a mutation that cannot be amplified by polymerase chain reaction would therefore remain undetected. Subsequent linkage and haplotype analyses should therefore be performed in some patients and efforts should be made to map the third LD locus. These results suggest that, despite advances in our understanding of the genetics of LD, skin biopsy remains a primary diagnostic modality and the current gold standard, since the number of different mutations is large and mutation detection requires genetic technology not routinely available outside research laboratories.

To the best of our knowledge, no direct association between these two rare diseases, congenital generalized lipodystrophy and LD, has been described. LD is a genetic disorder of carbohydrate metabolism, while lipodystrophy is associated with insulin resistance and its complications, though any interaction between their pathogeneses remains unclear. Some studies have shown that some functions of the endoplasmic reticulum, such as protein synthesis and the secretion and degradation of any misfolded proteins, may be deranged in hyperglycemic patients with lipodystrophies [25]. Interestingly, Lafora bodies are endoplasmic reticulum-associated polyglucosan depositions. Nevertheless, further studies are needed to clarify the relationship between these two diseases.

The prognosis of LD is presently poor, and treatment remains palliative. Antiepileptic drugs, including valproate, benzodiazepines (especially clonazepam), levetiracetam, piracetam and zonisamide are commonly used for the management of seizures and myoclonus. There is a risk of overmedication when treating drug-resistant myoclonus. Phenytoin, vigabatrin, carbamazepine, gabapentin, and probably lamotrigine, should be avoided to prevent worsening of myoclonus [26]. The promising ketogenic diet used for LD was not suitable for our lipodystrophic patient. Experiments to replace EPM2A using immunoliposomal vectors are currently in progress [22]. Better understanding of the pathogenetics of LD may allow the development of gene-replacement therapies, which could improve the prognosis for patients with LD.

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**REFERENCES**


Lafora 氏症合併先天性全身脂質營養不良症
－ 病例報告

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本文報告一 11 歲患先天性全身脂質營養不良症的男性病童於後児童期出現抽搐痙攣、肌陣攣、運動失調及認知功能衰退等症狀，皮膚切片發現汗腺有 Lafora 小體而診斷為 Lafora 氏症，做基因序列分析並未發現 EPM2A 及 EPM2B 之基因突變。之前的文獻並未報告過此類合併先天性全身脂質營養不良症與 Lafora 氏症的案例，而本病例為首例；至於兩者間是否有關聯性以及如何確認 Lafora 氏症的第三個基因位點仍待進一步的研究。

關鍵詞：Lafora 氏症，脂質營養不良症，肌陣攣，進行性肌陣攣癲癇症
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