LAFORA DISEASE AND DIABETE
Enlarging clinical phenotype

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Introduction

Lafora disease (LD) is rare, fatal, autosomal recessive progressive myoclonic epilepsy which results from carbohydrate accumulations in many tissues. We report a case of LD in a 14-year old adolescent associating aggravating neurological manifestations and non auto-immune diabetes.

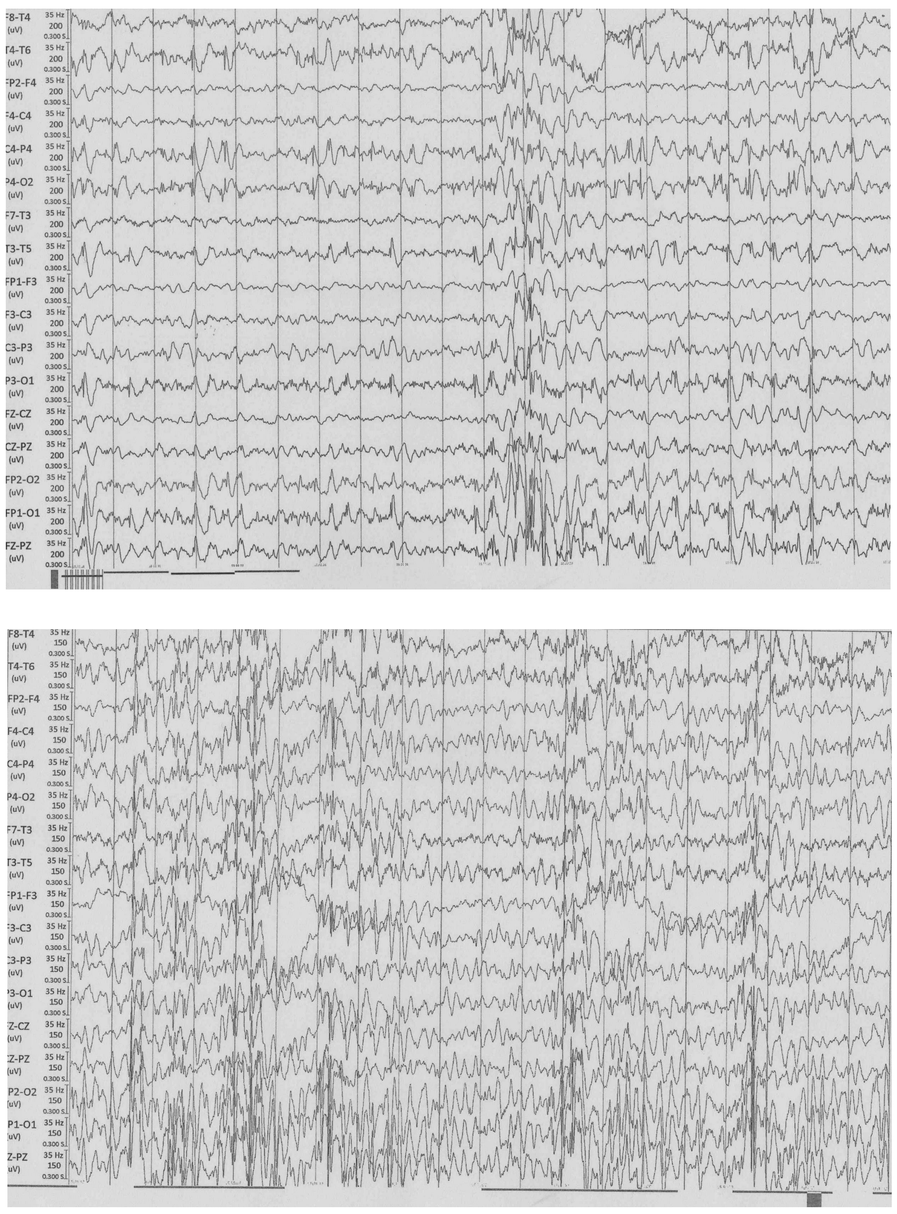

Figure: evolution of the electroencephalogram (EEG); above, initial EEG with paroxysmal generalized spike-waves complexes; below, EEG 2 years later with generalized slowdown associated with multiple paroxysmal complexes

Conclusion

Lafora disease is a progressive myoclonus epilepsy beginning in late childhood with a typical clinical course. Abnormal glycogen metabolism and autophagy account for multiorgan accumulation of Lafora bodies with neurodegeneration and possible functional consequences (insulin resistance). The glycemic disorders reported in our patient do not correspond to a type of diabetes known, a coincidence between these two pathologies remains so unlikely.

Case report

A 13-year-old boy was transferred to our department for evaluation and management of seizures. His personal and family medical history is unremarkable, particularly for neurologic or metabolic disorders. His physical exam was normal, but the electroencephalogram recording showed many subclinical, paroxystic and photosensitive generalized spikes waves. A multidrug therapy was initiated, with progressive clinical and electrical impairment (figure), and the diagnostic of progressive myoclonic epilepsy was suspected. Six months later, the diagnosis of non-autoimmune diabetes was made, requiring a very low dose of long-acting insulin. Testing for maturity onset diabetes of the young (MODY) found no mutations (table).
A retinal dystrophy was noted on electroretinogram and the skin biopsy found glycogen inclusions in the excretory ducts of eccrine sweat glands. Two years after the first signs of epilepsy, LD was confirmed with evidence of a c.386C> A p (Pro 129 His) mutation in the malin EMP2B gene. A new evaluation of pancreatic endocrine secretion showed a certain insulin resistance, with no pancreatic antibodies. Diabetes therapy was temporary switched to metformine, with satisfactory metabolic profile, but some side effects.

	Weights	Biological profile	Treatment	Remarks
At diabetes diagnosis (6 months after the first seizure episode)	45 kg	Blood sugar 200 mg/dl (60 – 100mg/dl) Insulin 15.7 mU/l (2 – 17 mU/l) C peptide 0.93 nmol/l (0.37 – 1.47 nmol/l) HbA1c 7.5% (4 – 6%) Negative autoimmune markers (ICA, GAD65, IAA, ZnT8)	Insulin basal-prandial regimen 0.25 units/kg/d	T1DM ?
3 months after diabetes diagnosis	45 kg	HbA1c 6%	Insulin (long-acting analogue) 0.2 units/kg/d	T1DM ?
6 months after diabetes diagnosis		No MODY mutations (GCK, HNF1A, HNF4A, HNF1B, ABCC8, KCNJ11, INS)	Insulin (long-acting analogue) 0.2 units/kg/d	T1DM ?
12 months after diabetes diagnosis	48 kg	HbA1c 6.5%	Neither insulin, nor other diabetes treatment	Diabetes mellitus, but not T1DM
Lafora diagnosis (24 months after the first seizure)	50 kg	Insulin 29.4 mUI/l C peptide 1.62 nmol/l (patient´s own secretion) HbA1c 8.2%	Metformin 1000 mg/d	Insulin resistance
36 months after diabetes diagnosis	52 kg	Blood sugar 200 – 300 mg/dl C peptide 1.8 nmol/l Negative pancreatic antibodies HbA1c 8.3%	Metformin 1500 mg/d	Insulin resistance/T2DM
40 months after diabetes diagnosis	52 kg	Blood sugar 170 – 200 mg/dl C peptide 0,9 nmol/l Insulin 12 mUI/l HbA1c 7,6%	Metformin 1000 mg/d	Insulin resistance/T2DM

Table: Patient's diabetes – insulin secretion and treatment ; T1DM – type 1 diabetes mellitus, HbA1c - glycated haemoglobin, ICA - islet cell antibodies, GAD65 - antibodies to glutamic acid decarboxylase, IAA - insulin autoantibodies, ZnT8 - zinc transporter 8 autoantibodies, MODY - maturity onset diabetes of the young, T2DM – type 2 diabetes mellitus