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A newly characterized HPDL-associated neurodegenerative disease: two cases representing the variability of clinical spectrum

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Background

Last year a new neurodegenerative disorder was described by two international collaborator groups. An association has been revealed between loss-of-function variants affecting the *HPDL* gene and a variable phenotype ranging from neonatal encephalopathy to adolescent-onset spastic paraplegia.

Here we further delineate the clinical course related to the disfunction of HPDL by characterization of two new patients and adding a less recognized clinical feature of ataxia which was present in one of our patients.

The patients were recruited in scientific research projects after clinical genetic testing failed to identify the cause of patients' clinical features. One patient was referred from Children's Clinical University Hospital (Latvia), and one from Centre Hospitalier du Quebec (Canada).

The genetic testing performed in this project involved *duo* and *trio* whole exome/genome sequencing (WES/WGS) analysis.

Case 1

CLINICAL A boy, 3 years old, pregnancy complicated by drug abuse.

Disease onset at 5 weeks: seizures, burst-suppression EEG pattern, elevated blood lactate (2.6–4.4 mmol/l)

2 months: sleep apnea and sinus bradycardia, presumably of central origin,

6 months: microcephaly,

Current status: spasticity, severe global developmental delay, and central blindness, recurrent episodes of anemia, feeding difficulties, scoliosis and hip luxation.

Mitochondrial respiratory chain enzyme analysis

– skin fibroblasts: reduced citrate synthase activity; no deficiency was observed before or after correction for citrate synthase activity.

– muscle: Citrate synthase activity mildly reduced; complex I reduction to 43% of mean - not diagnostic for a deficiency.

Brain MRI - diffuse and severe leukodystrophy, elevated lactic peak on MR spectroscopy.

Muscle biopsy - myopathic changes with predominant atrophy of oxidative fibers (type I and II), accumulation of free glycogen, capillary endothelium edema.

WES - homozygous variant c.1013T>C p.(Leu338Pro) in the *HPDL* gene.

Case 2

CLINICAL A boy, 11 years old, born postterm (42 gw).

Presented at 6 weeks of age, hypertonia and seizures. Treatment with valproic acid for one year, seizures never recurred.

Mildly delayed psychomotor development, increased clumsiness noted at 4 years.

At 6 years - spastic gait, hyperreflexia, polykinetic reflexes, intention tremor, dysarthria and intermittent enuresis. IQ - 70.

During next year he developed dysphonia, intention tremor, dysmetria, and gait ataxia.

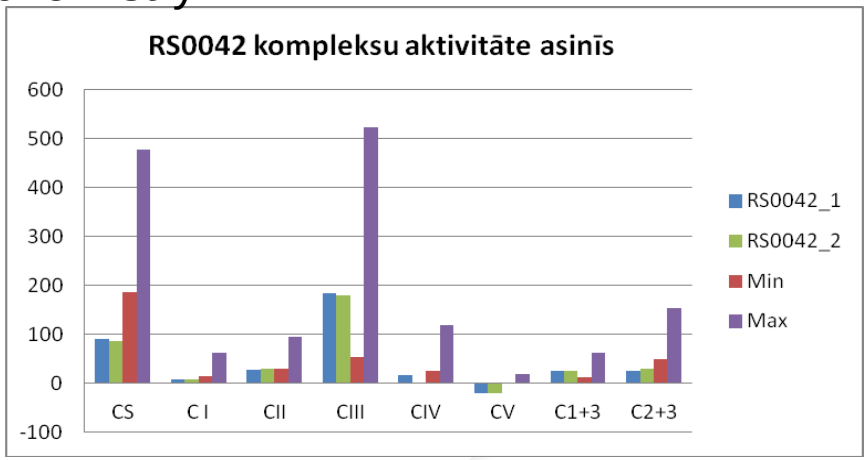
Lost ambulation at the age of 7.5 years.

No lactate or alanine elevations seen on blood biochemistry.

Brain MRI changes were attributed to hypoxic-ischemic encephalopathy. MR spectroscopy did not show elevation of lactate peak.

Mitochondrial respiratory chain enzyme analysis in blood – pronounced reduction of citrate synthase, low complex I and complex IV activities.

WGS - a homozygous variant c.599delG, (p.Gly200Alafs*4) in *HPDL* gene.



Conclusions

Our patients add to the 34 previously reported patients and represent the severe and intermediate range of the reported clinical spectrum.

In this report we also aimed to add a phenotypic feature that was not before recognized as a part of this syndrome. Mild gait ataxia has been noted only in one of the previously reported patients with a juvenile onset disease. However, our patient 2 developed neurological signs of cerebellar involvement at the age of 6 to 7 years, when the progressive disease course led to a more notable regression in motor and cognitive abilities.

The function of the *HPDL* encoded protein is yet unknown, however it has been shown to be expressed in multiple tissues, including brain, and to localize in mitochondria.

The mitochondrial OXPHOS complex activity analysis in both our patients show reduced citrate synthase and inconsistent reductions in complex I activity. The OXPHOS complexes were variably affected in previous reports.

As citrate synthase is a marker of intact mitochondria, it would be important to understand if its reduction reflects overall mitochondrial damage or the citrate synthase is itself affected by a pathway involving the *HPDL* product.