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Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL): report of a large new family.

A. Gai[1], E. Giorgio[2], A. Brusco[2], P. Ferrero[3], L. Pinessi[1], G. Vaula[3]
[1] Neurology I, Department of Neurosciences "Rita Levi Montalcini", University of Turin, Italy
[2] Medical Genetic Unit, Department of Medical Sciences – University of Turin, Italy
[3] Department of Neurosciences "Rita Levi Montalcini", Città della Salute e della Scienza University Hospital – Turin, Italy

Background

Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) [1] is a rare autosomal recessive neurological disorder caused by mutations in the DARS2 gene, encoding the mitochondrial aspartyl-tRNA synthetase [2].
The clinical course is characterized by progressive pyramidal, cerebellar and dorsal column dysfunction.
Radiological findings are pathognomonic [3].

Case report

A 33-year-old Romanian woman from non consanguineous parents was referred to our Clinic because of progressive walking impairment. She had a positive familial history.
Anamnestic data:

- urinary incontinence and impaired running since childhood
- spastic paraparesis and gait ataxia after pregnancies
- distal hypopallesthesia, upper limbs dysdiadochokinesia and dysmetria, absent deep tendon reflexes and equivocal plantar responses at the age of 33
- independent walking for less than 1000 m, Babinski sign and anapallesthesia at the age of 37

Methods

- Anamnestic data were collected from 11 siblings (5 affected)
- The patient and 6 siblings (4 affected) were neurologically evaluated.
- 3 affected underwent MRI and spectroscopy.
- The genetic analysis was performed on 8 subjects.

Results

Clinical features of affected siblings	♀Proband	♀1*	♂2*	♀3*
slight imbalance		X	X	
impaired running		X	X	
spastic paraparesis	XX▫			XX▫
gait ataxia	X			X
dysmetria	X			X
intention tremor	X		X	
dysdiadochokinesia	X	X		X
hypo/ana- pallesthesia	XX▫	X	X	XX▫
deep tendon reflexes (**A**bsent; **W**eak, **M**edium; **B**risk)	**A**	**M bicipital W patellar A ankle**	**B bicipital M patellar W ankle**	**M bicipital B patellar W ankle**
plantar response	**Babinski**	**normal**	**equivocal**	**Babinski**
dysphagia			X	X
urinary incontinence	X			X
eye movement defects (hypometric saccades, pursuit difficulties)			X	
foot deformities (pes cavus, hammertoe)	X	X	X	X

* Subject number
▫ Severe

1.5 T brain and spinal cord MRI with spectroscopy (Fig.1)

- Specific patterns of T2 and FLAIR hyperintensities
  - infratentorial (bulbar and pontine) white matter (WM) (a)
  - cerebellar WM, peduncles (b) and dentate nuclei (c)
  - lateral corticospinal tracts and dorsal columns (d)
  - intraparenchymal tracts of the trigeminal nerves (f)
- Spinal cord atrophy
- Lactate peak only in proband

Genetic analysis: DARS2 gene sequencing.

- Compound heterozygous mutations. (Fig.2)
  - c.228–20_21delTTinsC (p.Arg76SerfsX5)
  - c.788G>A (p.Arg263Gln)

Fig.1. LBSL disease: peculiar MRI pattern.

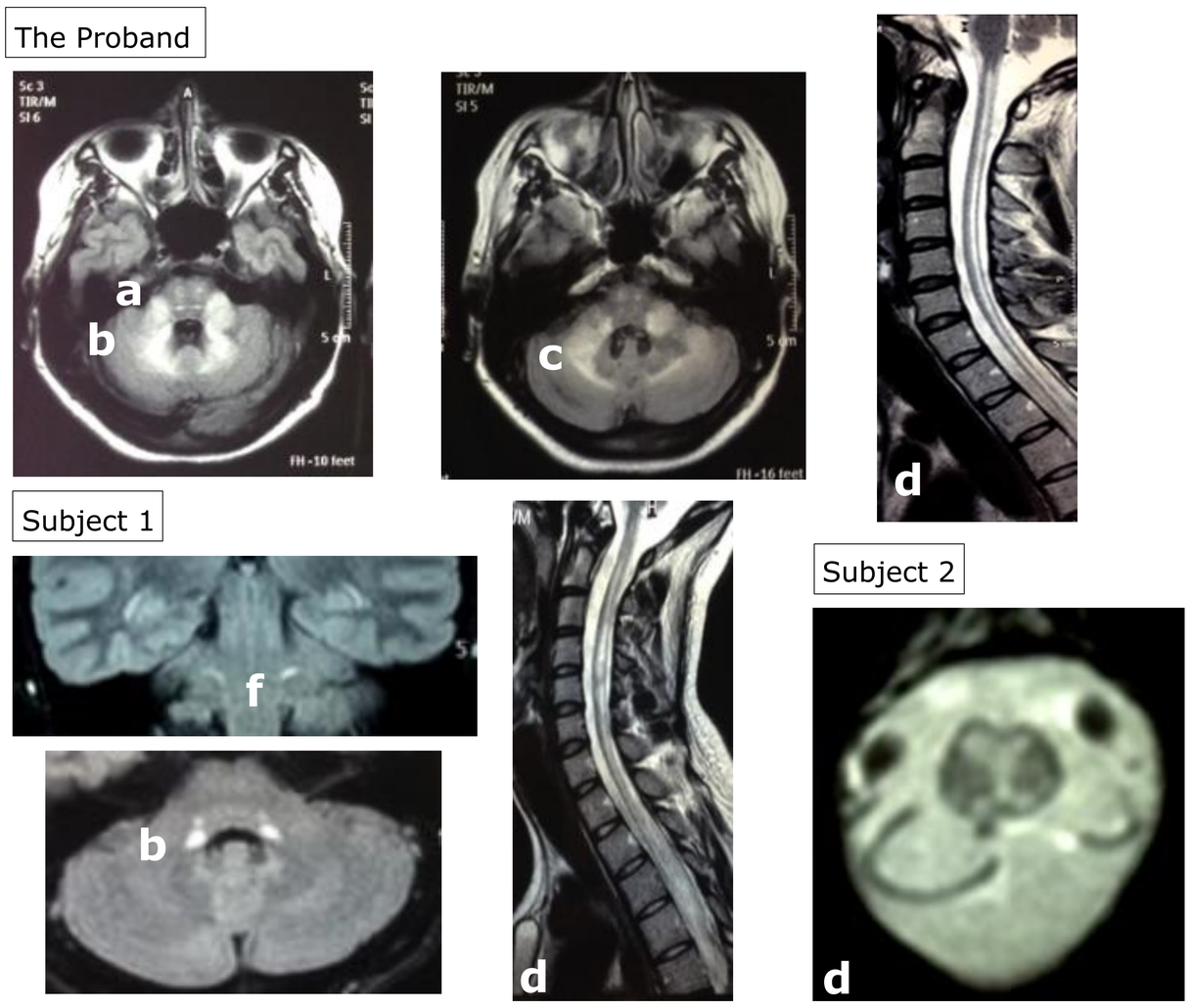
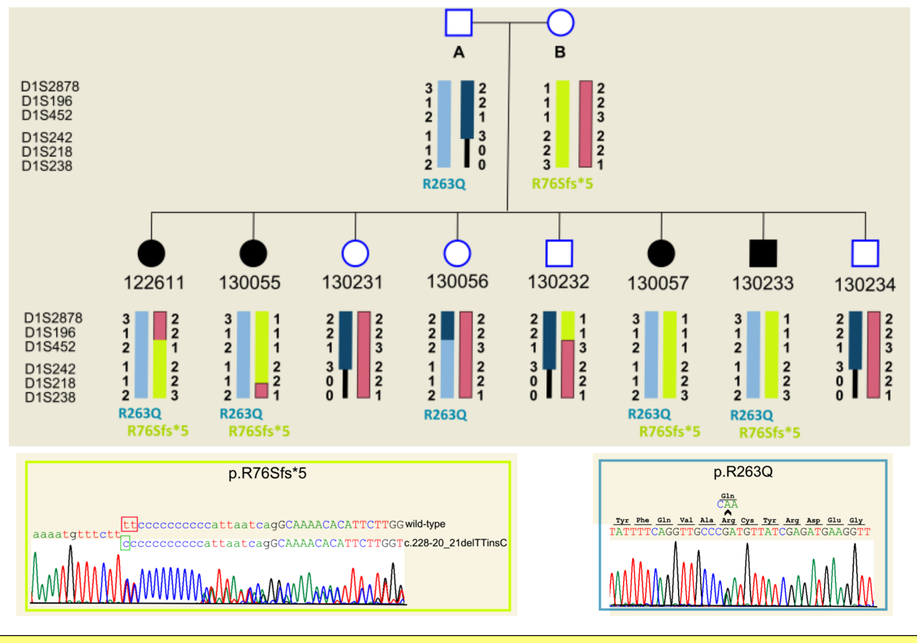


Fig.2. DARS2 gene sequencing: compound heterozygosity in 4 affected subjects.



Conclusions

- Our LBSL family carries two different mutations, both previously reported as pathogenic.
  - The first is the most common DARS2 intronic mutation and leads to frameshift and premature stop codon.
- Our pedigree confirms the intrafamilial phenotypic variability of this rare disorder.
  - An early-onset does not seem to lead necessary to severe disability.
  - Lack of lactate peak does not exclude the diagnosis, as previously described.
- Peculiar MRI features guide the physician to select patients for genetic analysis.
- LBSL must be taken in account in the differential diagnosis of longitudinal extensive transverse myelitis.

References

1. Van der Knaap MS, van der Voorn P, Barkhof F, et al. A new leukodystrophy with brainstem and spinal cord involvement and high lactate. Ann Neurol 2003;53:252–8.
2. Scheper GC, van der Klok T, van Andel RJ, et al. Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation. Nat Genet 2007;39:534–9.
3. Steenweg ME, van Berge L, van Berkel CG, et al. Early-onset LBSL: how severe does it get? Neuropediatrics 2012;43(6):332-8.