

matter. However, phenotypic manifestations are broad and include both *juvenile* and *adult* forms that often display infratentorial pathology and a paucity of leukodystrophic features. We describe the unique case of an 8.5 year old female who presented with an 8 month history of progressively worsening vomiting and cachexia, whose extensive multidisciplinary systemic workup, including GI biopsies, proved negative. Neuroimaging ultimately revealed bilaterally symmetric and anterior predominant supratentorial signal alterations in the white matter plus a 1.7 x 1.2 x 0.7 mm right dorsal medullary mass. Biopsy of this presumed low-grade glioma revealed features in keeping with AD, which was later confirmed on whole exome sequencing. The proband exhibited a pathogenic p.Arg239Cys heterozygous missense mutation in GFAP, which was apparently inherited from her asymptomatic mother (1% mosaicism in the mother's blood). Germline mosaic inheritance patterns of young-onset AD, particularly those presenting with a tumor-like mass of the brainstem, are scarcely reported in the literature and serve to expand the clinicopathologic spectrum of AD.

### LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Recognize an uncommon clinical presentation of AD.
2. Describe the underlying genetics of AD, including a rare familial juvenile onset form featuring germline mosaicism.

### ABSTRACT 7

#### Fetal neuroaxonal dystrophy: a further etiology of fetal akinesia

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Neuroaxonal Dystrophies (NAD) are neurodegenerative diseases characterized by axonal "spheroids" occurring in different age groups. The identification of mutations delineated new molecular entities in these disorders. We report neuropathological data of a new form of NAD, characterized by a precocious prenatal onset, different from classical and conatal Infantile Neuroaxonal Dystrophy (INAD).

We studied 5 fetuses examined after pregnancy termination and 2 term neonates deceased just after birth, 4/7 born from consanguineous parents. All subjects presented severe fetal akinesia sequence with microcephaly. In 4/7 cases, a molecular study was performed. In all cases, "spheroids" with typical immunohistochemical features were identified, with variable spreading in the central and peripheral nervous system. Basal ganglia, brainstem, cerebellum, and spinal cord involvement was constant. Associated CNS malformations, unusual in INAD, were associated including hydrocephalus (2), callosal agenesis/hypoplasia (2), olfactory agenesis (1), cortical (3) and retinal (1)

anomalies. None of the cases demonstrated mutations in PLA2G6, found in INAD. The clinical and neuropathological features of these fetal cases are different from those of "classical" INAD. The absence of mutations in PLA2G6, in addition, suggests that the fetal NAD is a new entity, distinct from INAD, with different molecular basis. Associated malformations suggest a wide phenotypic spectrum and probable genetic heterogeneity. Finally, fetal NAD is an additional etiology of fetal akinesia.

### LEARNING OBJECTIVES

This presentation will enable the learner to:

Diagnose this rare form of neuroaxonal dystrophy (NAD) occurring precociously, in the fetal life, as soon as the second trimester, different from the infantile form of NAD.

1. Describe the phenotypic spectrum of this fetal NAD; fetal akinesia sequence, microcephaly and various brain malformations, different from the "classical" and conatal forms of infantile neuroaxonal dystrophy.
2. Consider this etiology in the diagnosis of fetal akinesia sequence.

### ABSTRACT 8

#### A young woman with multiple acyl-CoA dehydrogenase deficiency (MADD)

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A 31-year-old female hairdresser whose parents were first degree cousins complained of episodic attacks of headache, vomiting, and dizziness for the past eight years after an uneventful childhood and adolescence. Four years ago, she developed progressive weakness, muscle pain and difficulties walking and lifting her arms that she could not work in her profession anymore. She lost hair, weight and became amenorrhoeic. Finally, her muscle weakness required intensive care. Early on her CK was mildly elevated to 237 U/l (normal < 167), but later to 900 and 1800. By MRI, skeletal muscles showed minimal contrast enhancement.

The clinically suspected diagnosis of myositis prompted repeated muscle biopsies, which disclosed non-specific myopathic changes, scattered necrotic muscle fibers without inflammation, protein aggregation, or vacuolation by light microscopy, but abnormally structured mitochondria with inclusions by electron microscopy, and treatment with steroids without any clinical improvement.

A panel of 1131 mitochondrial genes revealed a homozygous mutation in the *ETFDH* gene.

### LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Discuss MADD as a mitochondrial and lipid storage disease
2. Recognize the myopathology of MADD