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Abstracts

Articles appearing in the April 2018 issue

Diagnostic odyssey of patients with mitochondrial disease: Results of a survey

Objective To document the complex diagnostic odyssey of patients with mitochondrial disease.

Methods We analyzed data from 210 Rare Diseases Clinical Research Network Contact Registry participants who were patients with a biochemical deficiency or self-reported diagnosis of mitochondrial disease, or their caregivers.

Results Participants saw an average of 8.19 clinicians (SD 8.0, median 5). The first clinician consulted about symptoms was typically a primary care physician (56.7%), although 35.2% of participants initially sought a specialist. Of note, 55.2% of participants received their diagnosis from a neurologist, 18.2% from a clinical geneticist, and 11.8% from a metabolic disease specialist. A majority of the participants (54.6%) received 1 or more nonmitochondrial diagnoses before their final mitochondrial diagnosis. In their pursuit of a diagnosis, 84.8% of participants received blood tests, 71% a muscle biopsy, 60.5% MRI, and 38.6% urine organic acids. In addition, 39.5% of the participants underwent mitochondrial DNA sequencing, 19% sequencing of nuclear genes, and 11.4% whole-exome sequencing.

Conclusions The diagnostic odyssey of patients with mitochondrial disease is complex and burdensome. It features multiple consultations and tests, and, often, conflicting diagnoses. These reflect disease variety, diagnostic uncertainty, and clinician unfamiliarity. The current survey provides an important benchmark. Its replication at appropriate intervals will assist in tracking changes that may accompany increased popularity of exome testing, more rigorous diagnostic criteria, increased patient-reported outcome activity, and trials for promising therapies.

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Ataxia-telangiectasia: A new remitting form with a peculiar transcriptome signature

Objective Ataxia-telangiectasia (AT) is a rare, severe, and ineluctably progressive multisystemic neurodegenerative disease. Variant AT phenotypes have been described in patients with mild and late-onset neurologic deterioration and atypical features (dystonia and myoclonus). We report on the clinical characteristics and transcriptome profile of patients with a typical AT presentation and genotype who experienced an unexpected favorable course.

Methods A 24-year-old woman developed, by the age of 3 years, all the classic symptoms of AT associated with increased α-fetoprotein levels, a compound AT-mutated (ATM) genotype with an inframe deletion c.2250 G>A (*p*.Glu709_Lys750del42) and a missense mutation c.8122 G>A (*p*.Asp2708Gln), and no residual ATM protein expression. By age 12 years, ataxia slowly disappeared, and a very mild choreic disorder was the only neurologic feature in adulthood. Brain MRI was normal. The blood transcriptome profile was assessed and compared with that of healthy controls and patients with the classic AT phenotype.

Results The atypical clinical course of the patient was associated with a transitional transcriptome profile: while 90% of transcripts were expressed as in patients with the classic AT presentation, 10% of transcripts were expressed as in healthy controls.

Conclusions The unexpected mild clinical outcome and transcriptome profile of this patient with AT suggest the existence of individual resilience to the altered ATM synthesis. Because of their possible prognostic and therapeutic implications, the identification of modifier factors affecting the phenotype would deserve further studies.

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