

Prenatal Diagnosis of Infantile Neuroaxonal Dystrophy

Case Report

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Infantile Neuroaxonal Dystrophy (INAD1, MIM # 256600), is a rare autosomal recessive neurodegenerative disorder. The clinical picture is characterized by psychomotor regression and hypotonia, which progresses to spastic tetraplegia, visual impairment and dementia. Onset is within the first 2 years of life and death usually happens before the age of 10. In 2006, Morgan et al described that mutations in PLA2G6 gene localized in chromosome 22 (22q13), caused INAD1. Evidence showed that a large proportion of patients with infantile neuroaxonal dystrophy have a mutation in the PLA2G6 gene.

A 36-years-old pregnant woman presented for obstetric follow up. It was the second pregnancy of this healthy, nonconsanguineous couple. Their 7 year-old daughter was affected with Infantile Neuroaxonal Dystrophy. Molecular testing was done in the child and, as a causal mutation was detected, it was possible to offer a specific prenatal diagnosis. The molecular study of PLA2G6 gene by amniocentesis showed the presence of a mutation in heterozygosity and the karyotype was normal for a female foetus.

To our knowledge, this is the first molecular prenatal diagnosis of INAD1 in Portugal.

Key-words: neuroaxonal; dystrophy; PLA2G6.

ARQUIVOS DE MEDICINA, 24(3):89-90

INTRODUCTION

Infantile Neuroaxonal Dystrophy (INAD1; # 256600) is a severe and rapidly progressive neurodegenerative disease with an autosomal recessive inheritance. INAD comprises a classic and an atypical form. The classic form begins before age three with hypotonia, progressive psychomotor delay and symmetric pyramidal tract signs (strabismus, nystagmus and optic atrophy). The atypical form begins in early childhood with gait instability, ataxia, speech delay, autistic features with neurologic deterioration and extrapyramidal findings; neuropsychiatric disturbances including poor attention, hyperactivity and emotional lability are also common (1,2,3). Death usually occur before age of 10 (2). The hallmark of the disease is widespread focal swelling and degeneration of axons with scattered spheroid bodies in both central and peripheral nervous system (2,4). Cerebellar atrophy and signal hiperintensity in the cerebellar cortex on T2-weighted MRI images are characteristic but not pathognomonic (3,5). The differential diagnosis for childhood cerebellar atrophy includes neuronal ceroid-lipofuscinosis (Santavuori-haltia), ataxia-telangiectasia, and hereditary ataxia (1). Spheroids are found in brain in

other conditions, including PKAN, idiopathic NBIA, infantile GM2 gangliosidosis, Niemann-Pick disease type C, and Menkes disease (1). Fast rhythms on EEG were observed in all patients (6).

The frequency of INAD is unknown. Currently no effective treatment is available. Therapeutic approach involves treatment of manifestations for spasticity and seizures, control of secretions, prevention of aspiration pneumonia by feeding modifications, psychiatric support, prevention of secondary complications with physiotherapy and periodic assessment of vision and hearing (1).

The disease gene, PLA2G6 - the gene encoding phospholipase A2 group VI, was mapped in 2006 by Morgan et al to a 1.17-Mb locus on chromosome 22q13.1 (7).

METHODS

We present a 36-years-old pregnant woman, II Gesta I Para, healthy nonconsanguineous couple. Before this pregnancy they had preconceptional counselling as their 7-years-old daughter, was affected by Infantile Neuroaxonal Dystrophy. At that time, the molecular basis of the disease remained unknown. A few months later, when she got

pregnant, we confirmed the recent possibility of molecular testing. The results showed composed heterozygosity for 2 pathological mutations in the affected child (c.1442T>A and c.2370T>G). Based on this molecular characterization, it was possible to offer a specific prenatal diagnosis and an amniocentesis was performed.

RESULTS

The karyotype was normal for a female foetus and molecular study of PLA2G6 gene showed the presence of the mutation c1442T>A in heterozygosity, which was compatible with a status of a healthy carrier. Pregnancy was uneventful.

At 39th weeks, due to oligoamnios, labour was induced with a vaginal delivery of a healthy girl (2990 g, 48 cm and 9/10 Apgar score).

DISCUSSION

Authors emphasize the role of preconceptional counselling in identification and orientation of couples with genetic risk. Diagnosis of familiar diseases allows a correct genetic counselling and in many cases the possibility of a specific prenatal diagnosis in future pregnancies, allowing couples informed decisions. Molecular prenatal diagnosis is the best approach if a mutation within the family is identified in a timely manner.

Authors highlight the need of a continuous actualization, involving each member of a prenatal diagnosis team, taking in account the fast evolution of Genetics field.

To our knowledge this case documents the first molecular prenatal diagnosis INAD in Portugal.

The molecular analysis of the affected sister was done at the Medical Institute of Genetics of OPorto with probes provided by the laboratory Molecular & Medical Genetics (Dr Susan Hayflick) - Oregon Health & Science University - Portland - USA.

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