AN UNUSUAL PRESENTATION OF SYNE1 MUTATION (ARCA1 - BEAUCE ATAXIA-SCAR8): HYPOGONADISM AND INTELLECTUAL DISABILITY

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Introduction

Syne1 gene is one of the biggest genes in the human genome and includes 146 exons. Its mutation was originally described as a pure form of cerebellar ataxia but recent studies showed that only 20% of the patients have a pure phenotype.
Aim of this study is to describe the atypical phenotype in two patients from a consanguineous marriage carrying a homozigous truncating mutation in Syne1/nesprin1 gene.

Methods

21 ataxic patients who tested negative for pathological expansions in SCA1,2,3,6,7,17 and for the intronic GAA and for the intronic GAA expansion in FXN were analyzed using a customized target next-generation resequencing (NGS) panel able to invetsigate the coding region of 82 genes linked to ataxia. Data were analyzed using Ingenuity Variant Analysis software. Mutations were confirmed by Sanger sequencing

CLINICAL FEATURES	PATIENT 1	PATIENT 2
SEX	MALE	FEMALE
ONSET	2 YEARS	24 YEARS
DISARTHRIA	YES	YES
ATAXIA	YES	YES
NEUROPATHY	NO	NO
REFLEXES	BRISK	BRISK
EYE MOVEMENT	FRAGMENTED SMOOTH PURSUIT	SLOW, HYPOMETRIC SACCADE
TREMOR	POSTURAL	POSTURAL
HORMONAL PROFILE	LOW LEVEL TESTOSTERON	HYPERGONADOTROPIC HYPOGONADISM
MRI CEREBELLAR ATROPHY	MARKED	MARKED
ADDITIONAL FEATURES	PSYCHOMOTOR RETARDATION DYSTONIA	COLD EXTREMITIES DYSTONIA

Table 1: Clinical features of patients

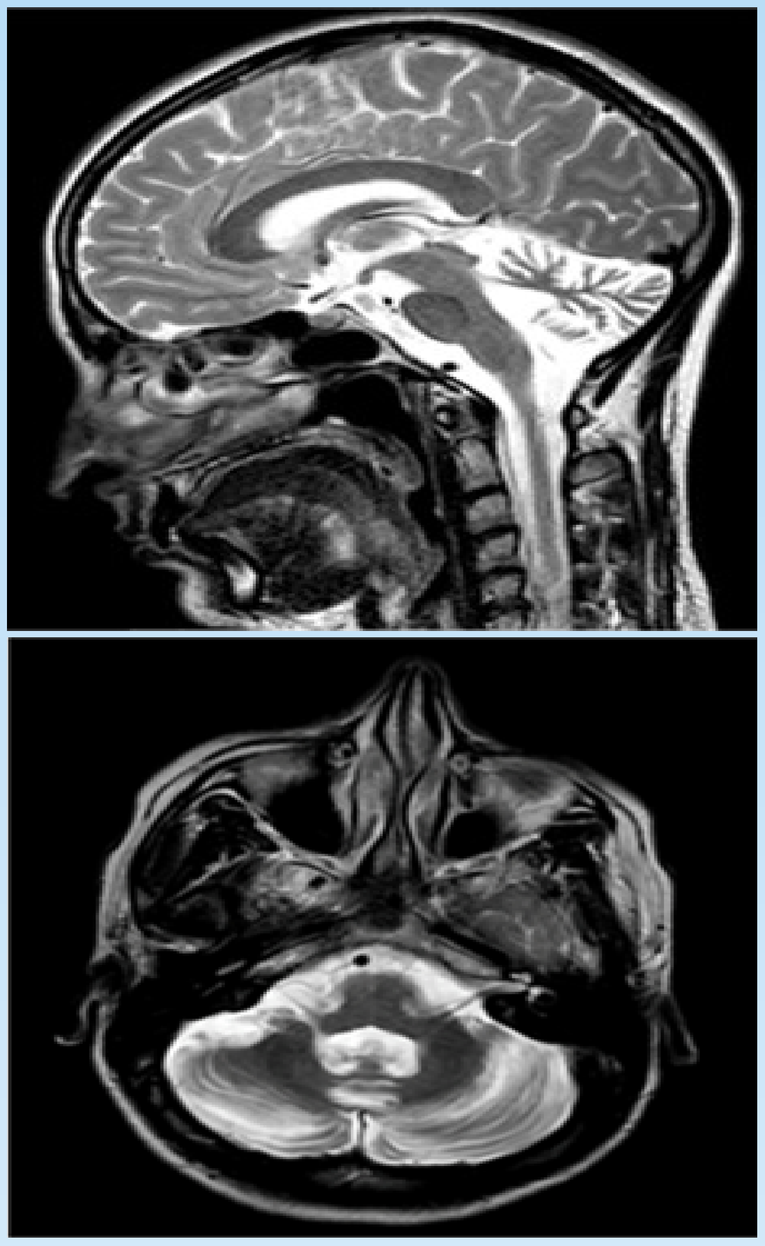

Fig.1 MRI T2 Sagittal and Coronal slice showing cerebellar *atrophy*

Results

A certain diagnosis was reached in 1/3 of the patients. The proband born from a consanguineous marriage carried a homozygous mutation c.4609C>T in the Syne1/nesprin1 gene. Both parents were carriers and the affected brother was homozygous for the same mutation. This mutation has not previously reported. The patient 1 was a 36-years-old woman with onset at 24. She has slight ataxia, marked disarthria, brisk knee jerks, normal nerve conduction study, marked cerebellar atrophy and hypergonadotropic hypogonadism. The patient 2 was a 39-years old male with psychomotor retardation and showed mild ataxia, intellectual disability, low level testosteron with normal gonadotropin, normal nerve conduction and marked cerebellar atrophy (Table 1)

CONCLUSIONS

Syne1 gene should be considered in the screening of hereditary ataxia. Mental retardation is rarely reported while hypogonadism has never been reported

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