Case Report

Novel Autosomal Recessive c10orf2 Mutations Causing Infantile-Onset Spinocerebellar Ataxia

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Received 11 June 2012; Accepted 5 July 2012

Academic Editors: N. Arslan and L. B. Rorke-Adams

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Recessive mutations in genes encoding mitochondrial DNA replication machinery lead to mitochondrial DNA depletion syndromes. This genetically and phenotypically heterogeneous group includes infantile onset spinocerebellar ataxia (OMIM# 271245) a neurodegenerative disease caused by mutations in the mtDNA helicase gene, c10orf2, with an increased frequency in the Finnish population due to a founder mutation. We describe a child of English descent who presented with a severe phenotype of IOSCA as a result of two-novel mutations in the c10orf2 gene. This paper expands the phenotypic spectrum of IOSCA and adds further evidence for the presence of a genotype-phenotype correlation among patients with recessive mutations in this gene.

1. Introduction

Mitochondrial recessive ataxia syndromes caused by mutations in c10orf2, which encodes mitochondrial DNA (mtDNA) helicase, and in POLG1, which encodes mitochondrial DNA polymerase, can result in abnormal mtDNA replication leading to depletion in copy number. Mitochondrial DNA depletion results in a neurodegenerative course in infantile-onset spinocerebellar ataxia (IOSCA) (OMIM# 271245) caused by mutations in c10orf2, and in mitochondrial spinocerebellar ataxia epilepsy syndrome (MSCAE) (OMIM# 607459) and Alpers-Huttenlocher syndrome (OMIM# 203700) both caused by mutations in POLG1 [1]. IOSCA is characterized by a period of normal development for approximately the first year of life followed by development of ataxia, hypotonia, loss of deep-tendon reflexes, and athetosis. Signs of advanced disease include ophthalmoplegia, sensorineuronal hearing loss, sensory axonal neuropathy, and epilepsy [2]. This condition was first described in Finland due to a homozygous founder mutation (1708A > G, Y508C) [3]. Other diseases causing mutations in the c10orf2 gene have been reported subsequently [4–6]. Here we describe a child of English descent presenting with a phenotype of IOSCA who was found to be a compound heterozygote for two previously unreported presumed pathogenic mutations in the c10orf2 gene.

2. Case Presentation

The propositus attained fine and gross motor milestones at appropriate ages until 8 months of age, at which time she began to regress. By 13 months she had lost her ability to control her head and could no longer sit independently or roll. She continued to achieve purposeful hand movements and was able to pick up small objects albeit with some difficulty.

She was the first born to a healthy-27-year-old mother and a healthy-29-year-old father, both of English ancestry. The pregnancy was unremarkable with no history of exposure to teratogens. The perinatal and neonatal histories were remarkable. Her birth weight was 3.615 kg (75th percentile), her length was 52.25 cm (75th percentile), and her OFC was 34.5 cm (50th percentile). Her Apgar scores were nine at one and at five minutes. The family history was unremarkable for neurodegenerative disease and consanguinity.
The physical examination at 14 months revealed a non-
dysmorphic child. Her weight was 9.31 kg (40th percentile),
height was 77 cm (50th percentile), and her OFC was
44.75 cm (2nd percentile). Cranial nerves examination was
remarkable for conjugate eye movements with incon-
sistent and variable nystagmus. Her fundus examination
was normal. Her facial movements were symmetric. She
had dyskinetic tongue movements and drooling. Her head
control was fair and her muscle strength was within normal
limits. She had significant hypotonia in both her trunk
and limbs to passive movement but increased tone on
vertical suspension. Her deep tendon reflexes were not
elicitable and her plantar responses were flexor. She exhibited
choreoathetoid movements in her limbs and marked truncal
unsteadiness.

Her neurodevelopmental status remained stable with no
further regression over the course of the following year. At
four years of age, she developed numerous clinical and elec-
trographic seizures and subsequent epileptic encephalopathy.
At this age her physical examination revealed the presence of
ophthalmoplegia.

Investigations including plasma, urine and cerebrospinal
fluid amino acids, urine organic acids, plasma ammonia,
serum carnitine levels, acylcarnitine profile, transferrin iso-
lectric focusing, lysosomal enzyme assay panel, plasma very
long chain fatty acids, urine creatine and guanidinoacetate,
screening for neuronal ceroid lipofuscinoses types 1 and
2, and screening for Niemann-Pick disease types A, B, and
C failed to yield a diagnosis. Capillary lactate levels were
inconsistently elevated, ranging from 0.6 to 5.3 mmol/L
(normal range: 0.55–2.2), while the CSF lactate was normal.
Serum alpha-fetoprotein was elevated ranging from 16 to
31 μg/L (normal range: 0–7.0). Liver transaminases were
normal. A karyotype analysis and molecular testing for
Angelman syndrome, Rett syndrome, and ataxia with
oculomotor apraxia type 2 were unrevealing. Respiratory
chain enzyme analyses and histopathologic examination of
muscle were nondiagnostic. Magnetic resonance imaging of
the brain at 12 months of age was normal, but subsequent
imaging showed increased prominence of the extra-axial
spaces and evidence of atrophy. Nerve conduction studies
revealed evidence of sensory neuropathy.

At age 5 years, her symptoms and signs worsened. Liver
transaminases were elevated; AST was 280 μ/L (normal range
10–50) and ALT was 123 μ/L (normal range 4–30). Given the
development of seizures, encephalopathy, ophthalmoplegia,
intermittently elevated capillary lactate, and elevated liver
transaminases, a mitochondrial DNA depletion syndrome
was considered. POLG1 mutation analysis was unrevealing.
Sequencing of the c10orf2 gene (Centogene GMBH) revealed
two previously undescribed nucleotide changes, c.247C > T
(P83S) and c.1387C > T (R463W). The P83S alteration
occurs in the primase domain, and the R463W alteration
occurs in the helicase domain (Figure 1). Both alterations
occur in highly conserved regions and software analyses
with PolyPhen [7], SIFT [8], and AGVGD [9] support their
pathogenicity. The parents were shown to be carriers for one
mutation each.

At 5 years of age, the child passed away due to bron-
chopneumonia. Autopsy revealed neurodegenerative disease
characterized by mild cerebral atrophy, moderately severe
neuronal loss in the cerebellar dentate nucleus, and infer-
ior olivary nucleus of the medulla oblongata. Symmetric
hypertrophic endothelial changes with reactive astroglial
and microglial changes were present in the thalamus,
superior, and inferior colliculi. The cerebellar white matter
showed similar vascular changes and cavitation akin to
those seen in Leigh’s encephalopathy. Axons were lost from
the posterior columns of spinal cord and posterior roots.
Ultrastructural examination showed lipid droplets in the
endothelial cells and moderately severe peripheral axon loss
in the femoral and sural nerves (Figure 2). Skeletal muscle
had secondary neurogenic changes and mild fibre type 2
atrophy. These neurodegenerative changes were considered
to be attributable to a mitochondrial disorder.

3. Discussion

The girl described herein presented at 8 months of age with
a severe and progressive neurological phenotype suggestive
of IOSCA and was shown to have two-novel mutations in
the c10orf2 gene; c.247C > T (P83S) and c. 1387C > T
(R463W). The P83S alteration occurs in the primase domain
(Figure 1) in a highly conserved position and is predicted
to be pathogenic based on analyses with PolyPhen [7], SIFT
[8], and AGVGD [9]. The R463W alteration occurs in the
helicase domain (Figure 1) in a highly conserved position
and software analyses have also suggested that it is likely
pathogenic. The asymptomatic parents were each shown to
harbor one of these mutations, adding further support to the
pathogenicity.

Most reported recessive c10orf2 mutations are the result
of homozygosity for the Y508C Finnish mutation [3]. IOSCA
however has also been reported in non-Finnish individu-
als due to other mutations including Y508C/A318T [4],
Y508C/R29X [6], and T451I/T451I [5] (Figure 1). Whereas
dominant mutations, causing progressive external ophthal-
molplegia and mtDNA deletion tend to cluster in the linker
region of the Twinkle protein, recessive mutations causing

Figure 1: Schematic representation of the c10orf2 gene showing the locations of previously reported recessive mutations: (i) Y508C [3], (ii) A318T [4], (iii) T451I [5], (iv) R29X [6], and (v) P83S/R463W [Current paper].
Figure 2: Pathologic findings. (a) Photograph of horizontal slice through right cerebellum and medulla showing irregular region of atrophy (arrows) in white matter lateral to the dentate nucleus. (b) Photomicrograph of cerebellum showing regional loss of myelin surrounding a cavity (arrows). (Solochrome cyanin/eosin stain; original magnification 12.5x.) (c) Photomicrograph of plastic-embedded sample of cerebellar lesion showing hypertrophic endothelium (arrow) and macrophages (*) with vacuolated cytoplasm. (Toluidine blue stain; original magnification 600x.) (d) Electron micrograph of capillary endothelium (* shows lumen) in frontal lobe showing lipid droplet (arrow) (original magnification 80000x). (e) Photomicrograph of spinal cord showing loss of myelin staining and atrophy of posterior columns (arrow). (Solochrome cyanin/eosin stain; original magnification 12.5x.) (f) Photomicrograph of plastic-embedded sample of sural nerve showing moderately severe loss of myelinated axons (residual axons appear as dark rings; arrows). (Toluidine blue stain; original magnification 600x.)
DNA depletion tend to cluster in the helicase or primase domains [10] (Figure 1). Our patient has two presumed pathogenic mutations, one in the primase domain of exon 1 and one in the helicase domain in exon 2. Recently, Goh and coworkers described a girl with mutations in the primase and helicase domains; she presented at 2 months of age with acute liver failure, abnormal neurologic examination, and Fanconi syndrome, and died at 6 months of age [6]. Considering that the primase domain's role is localizing the helicase to its target, we anticipate that mutations in this domain significantly impact the helicase function, hence resulting in a severe phenotype.

Lonnqvist and coworkers suggested that patients who are compound heterozygotes for Y508C or have two other pathogenic mutations have a severe phenotype compared to Y508C homozygotes [1]. These patients present around six months of age, rather than after one year of age and manifest abnormal liver transaminases [1, 4–6]. In vivo studies have shown abnormal helicase function in patients homozygous for T451I as compared to normal function in Y508C homozygotes [5] further demonstrating the severity of other genotypes.

The pathologic changes in our patient are not identical to any reported cases. The asymmetric atrophic vascular hypertrophy changes in the thalamus and brainstem with pronounced cerebellar white matter involvement are histologically similar to those in Leigh's encephalopathy, but differ in localization. The abnormalities in the brain and spinal cord of previously reported children [11, 12] and one adult [13, 14] with POLG1 mutations have some pathologic features similar to this patient. The dentate nucleus and posterior spinal cord changes of one child with two c10orf2 mutations are also similar to our case [4]; however these changes do not appear to be pathognomonic for this condition [1, 6].

This paper further expands the phenotypic spectrum of c10orf2 gene mutations and adds further evidence for the presence of a genotype-phenotype correlation among patients with IOSCA.

References

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