Spastic paraplegia, optic atrophy, microcephaly with normal intelligence, and XY sex reversal: a new autosomal recessive syndrome?

Ahmad S Teebi, Steven Miller, Harry Ostrer, Patrice Eydoux, Céline Colomb-Brockmann, K Oudjhane, G Watters

Abstract

Two female sibs of first cousin Iranian parents were found to have the syndrome of spastic paraplegia, optic atrophy with poor vision, microcephaly, and normal cognitive development. Karyotype analysis showed a normal female constitution in one and a male constitution (46,XY) in the other. The XY female showed normal female external genitalia, normal uterus and tubes, and streak gonads. SRY gene sequencing was normal. We conclude that the present family probably represents a new autosomal recessive trait of pleiotropic effects including XY sex reversal and adds further evidence for the heterogeneity of spastic paraplegia syndromes as well as sex reversal syndromes.


Keywords: spastic paraplegia; optic atrophy; microcephaly; sex reversal

Hereditary spastic paraplegia (HSP) is a heterogeneous group of spinocerebellar degeneration disorders that are classified as non-syndromic, "pure", and syndromic. The non-syndromic form is usually autosomal dominant (MIM 182600); however, autosomal recessive and X linked recessive forms exist. The syndromic forms have been variably associated with ataxia, optic atrophy, extrapyramidal abnormalities, muscular dystrophy, and mental retardation. Less common associations include ichthyosis, vitiligo, premature greying of hair, retinal dystrophy, and brachydactyly, among others. Syndromic HSP is often considered to be autosomal recessive and appears to be more frequent in Middle Eastern populations. Sex reversal syndromes also constitute a heterogeneous group and include syndromes with and without involvement of the SRY gene, which is implicated in male differentiation.

We report two sisters of consanguineous parents with infantile onset spastic paraplegia, optic atrophy, microcephaly with normal cognitive development, and XY sex reversal in one.

Case reports

PATIENT 1

This patient was one of female twins; the other was stillborn with no obvious anomalies. The pregnancy was otherwise uneventful and delivery was normal at term in Iran. Birth weight was 2750 g and birth length was 50 cm. There were no neonatal problems. At the age of 6 months the parents noticed that she had a problem with tone and posture. Though she could roll over at 6 months of age, she was unable to support herself sitting. On evaluation at the age of 1 year she was found to have a normal CT scan of the brain and was diagnosed as having spastic diplegia. She could communicate well and cognitive skills appeared normal.

On examination at 4 years 4 months of age she appeared an alert and pleasant child with an occipitofrontal circumference (OFC) of 44.5 cm (<5th centile) and a length of 87 cm (<5th centile) (fig 1). She was unable to get into a sitting or standing position independently, but was able to crawl. She was not dysmorphic and the skin showed a small hypopigmented area on the right thigh and an extensive Mongolian spot on her back. She spoke with some dysarthria in French and her native language. There was plagiocephaly with flattening of the left part of the occiput and prominence of the left ear. Ocular movements were full and she followed light but had markedly reduced vision. Hearing was nor-

Figure 1  Patient 1: note the spastic posture. (Photographs reproduced with permission.)
There was no drooling. Stretch reflexes were brisk in the upper limbs and markedly brisk with clonus in the lower limbs. The extensor plantar responses were present bilaterally. Tone in all four extremities was increased. She had adductor spasm with scissoring and extensor thrusts of the lower extremities as she was placed in the standing position. There was difficulty with use of the upper limbs with grasp deficiency bilaterally. There was mild dystonic posturing of the hand when trying to reach for objects.

An MRI scan showed only a possible reduction in the size of the optic nerves bilaterally (fig 2). Ophthalmologic examination also showed small optic nerves suggestive of optic atrophy with no pigmentary retinopathy and normal maculae. Electroretinogram (ERG) and visual evoked responses (VER) suggested normal retinal function and an optic nerve conduction defect. Skeletal survey showed bilateral coxa valga and no brachydactyly or cone shaped epiphyses. The karyotype was 46,XY. Pelvic ultrasound showed an infantile uterus and virtually no gonads were identified (fig 3). At 5 years of age she underwent diagnostic laparoscopy, which showed a normal uterus, and laparotomy with excision of streak gonads. Histopathological examination of specimens from both sides showed no evidence of normal ovarian or testicular tissues. Some nodular microscopic calcifications were noted. Hormonal profile before surgery showed that LH was <1.5 U/l (normal 0-2), FSH 23.5 U/l (normal 0-5), testosterone 0.5 mmol/l (normal 0-2), and dihydrotestosterone 0.75 mmol/l (normal 2.2-10.3). Electromyography and motor and sensory nerve conduction studies were normal. Somatosensory evoked responses were suggestive of an abnormality rostral to the dorsal column nuclei, most likely in the thalamocortical projections bilaterally. Auditory brainstem evoked responses showed normal brainstem conduction. Electroencephalogram showed focal epileptiform activity over the right occipital region as well as poor development of background for age, suggesting a moderately diffuse disturbance of cerebral activity. Urine organic acids were unremarkable with absence of 3-methylglutaconic acid.

PATIENT 2

This patient was born normally after 37 weeks of an unremarkable pregnancy. Birth weight was 2650 g and birth length was 48 cm. There were no neonatal complications. Like her sister, she was noted to have problems with tone and posture at 6 months of age. On evaluation in Iran she was found to have a normal CT scan of the brain at 1 year of age and was diagnosed with spastic diplegia. She could communicate well with only slightly delayed language milestones. Cognitive skills were otherwise normal.

On examination at 2 years 6 months of age, her OFC was 43 cm (<5th centile) and her height was 80 cm (<5th centile) (fig 4). She was alert and responsive. She had soft, cup shaped ears and her skin showed five small café au lait spots with no axillary or inguinal freckling. Ocular movements were full and she had normal facial movement with no drooling. Stretch reflexes were brisk in the upper limbs and brisker in the lower limbs with some clonus at the ankles. Tone was increased in all four extremities, particularly in the legs. She could not sit or stand independently. She had adductor spasm with scissoring and standing on tiptoes when placed upright.

An MRI scan, like her sister, showed only a possible reduction in the size of the optic nerves bilaterally, but her vision was less affected. Ophthalmologic examination also showed small optic nerves suggestive of optic atrophy. Flash visual evoked responses suggested normal retinal function and an optic nerve conduction defect. Skeletal survey showed bilateral coxa valga. Karyotype analysis was normal. Pelvic ultrasound showed a prepubertal uterus and normal ovaries. Electroencephalography and motor and sensory nerve conduction studies were normal. Somatosensory evoked responses were suggestive of an abnormality rostral to the dorsal column nuclei, most likely in the thalamocortical projections bilaterally. Auditory brainstem evoked responses were normal. Electroencephalogram showed an abnormal pattern of
reactivity of uncertain significance. Urinary organic acids were unremarkable with absence of 3-methylglutaconic acid.

At 4 years of age, OFC was 44.4 cm (<5th centile) and height was 85 cm (<5th centile). There were no cranial nerve abnormalities. Plantar responses were extensor bilaterally. She reached for objects awkwardly but better than her sister. Apart from short stature, the general medical examination was unremarkable.

FAMILY HISTORY

The probands were the second and third of three daughters of phenotypically normal Iranian parents who are first cousins. Their first pregnancy was a normal female. Neurological examination of the parents and their first child was unremarkable. There is no family history of neuromuscular disease, poor vision, female infertility, or other defects.

CYTOGENETIC AND MOLECULAR CYTOGENETIC INVESTIGATIONS

G banded chromosomes in peripheral blood of patient 1 showed a 46,XY constitution. This was confirmed by high resolution G banding and fluorescence in situ hybridisation (FISH) probes specific for the X and Y centromeres (ONCOR). FISH probes from Xp21 were also used, which showed no duplication in this segment. Her sister's (patient 2) G banded chromosomes showed a 46,XX normal female constitution. The parents' chromosomes were normal.

SRY STUDIES

Genomic DNA was extracted from the blood of the two patients, their parents, and their normal sister. PCR was conducted with primers that amplify the SRY open reading frame, plus about 90 bp upstream of start codon and 70 bp downstream of stop codon. The PCR results were as expected from the karyotypic data. Only patient 1 and her father amplified the SRY region. Patient 1’s SRY PCR product was subsequently cloned into vector pCRII and sequenced. The sequence showed no difference from the SRY published sequence. The results suggest that the patient’s gonadal dysgenesis cannot be accounted for by a mutation in SRY.

Discussion

Syndromic or complicated HSP is a relatively common group which includes individually rare, clinically and genetically diverse disorders that have in common spasticity affecting predominantly the lower extremities. Optic atrophy is a frequently encountered association14–17 with additional peripheral neuropathy18 or ataxia, as in Behr’s syndrome.19–20 Patients with this disorder have excessive excretion of 3-methylglutaconic acid and 3-methylglutaric acid in their urine.20 Mental retardation (MR) is also a common finding in many HSP syndromes9–17 21–23 with additional cutaneous pigmentation disorder,24 transverse limb defects,25–26 or retinal dystrophy.27 Other individual syndromes include HSP with MR, retinitis pigmentosa,28 and deafness,29 HSP with peripheral neuropathy and painless foot ulcers,30 HSP with disordered pigmentation, peripheral neuropathy, and normal intelligence31 and with ataxia,32 HSP with vitiligo, premature hair greying, peculiar facies, and normal intelligence,33 HSP with congenital ichthyosis,34 the syndrome of HSP, brachydactyly, cone shaped epiphyses, and normal intelligence or Fitzsimmons syndrome,35 36 and others.3–5 7 11 40

A significant overlap exists between some HSP syndromes, such that two or more of the so called new syndromes represent a single entity. The majority of these syndromes are autosomal recessive, many of which have been described in Arab families or Jews originating from Arab countries who often have high frequencies of consanguineous marriages.20 24–26 30–33 35 However, in a few syndromes the inheritance is probably X linked recessive.18 19 21 23 41 42

However, the development of sex reversal in XY females may be the result of interference with testicular differentiation. This process is controlled mainly by the testicular determining factor (TDF) locus on distal Yp, which is the sex determining region Y (SRY), in addition to other genes located on the X chromosome and autosomes.13–17 Mutations in SRY, however, only account for about 20% of cases of XY gonadal dysgenesis.12–18 There is also evidence of an Xp region that can suppress testicular development in the presence of normal SRY.19–21 Many cases have been documented and the sex reversal associated with the presumptive locus appears to be the result of duplication and not disruption.45–46 This locus was assigned to a region on distal Xp21 adjacent to the adrenal hypoplasia congenita critical region and has been termed “DSS”
(dosage sensitive sex reversal). 67 There is clear evidence now for an important locus involved in testicular development from studying campomelic dysplasia patients with chromosomal rearrangements involving 17q24-25 or without chromosomal rearrangements but with mutations of the SOX9 gene. 68 Other loci have also been implicated. 13, 17, 18

The constellation of spastic paraplegia, optic atrophy, dystarthisia, and microcephaly with normal intelligence in two phenotypically female patients, with XY gonadal dysgenesis in one, is unlikely to be fortuitous. It may represent, however, a previously unrecognised syndrome, either in the category of syndromic HSP or XY sex reversal syndromes. The presence of parental consanguinity and the involvement of sibs of both genotypes is suggestive of an autosomal recessive trait with pleiotropic effects including XY sex reversal. This indicates that more loci are involved in testicular differentiation. We concur with Ferguson-Smith and Goodfellow 69 that future identification and cloning of genes that regulate SRY, and are regulated by SRY, will be facilitated by careful clinical analysis of sex reversed patients like this.

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