Familial unilateral Brown syndrome

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We present a two-generation family with Brown syndrome. The proband was a six and a half-year-old female who presented with a history of failure of dextro-elevation of her left eye. A full ophthalmic evaluation was consistent with a left Brown syndrome. Family history revealed that her mother was operated on as a child for left Brown syndrome and examination of her four and a half-year-old sibling showed similar affection in the left eye. Autosomal dominant inheritance has been postulated in this condition. To our knowledge this is the first report of three members of a two-generation family with left-sided Brown syndrome. Genetic counseling of Brown syndrome cases is advised; nevertheless, identification of the responsible gene should shed more light on its genetics.

Key words: Familial Brown syndrome

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The clinical entity commonly known as Brown syndrome was initially described in 1949 by Harold Waley Brown as superior oblique tendon sheath syndrome (SOTSS)[1] and is characterized by restricted passive elevation of the eye in the nasal field. Although usually sporadic, several reports describe either unilateral or bilateral Brown syndrome in siblings[2-5] including monozygotic[6,7] and dizygotic twins[8] suggesting possible autosomal recessive or dominant inheritance with reduced penetrance. Other reports have also described Brown syndrome in two-generation families[2,8,9] compatible with autosomal dominant inheritance with either one or both eyes affected without identical laterality. Interestingly, Iannacone *et al.*,[5] described left unilateral Brown syndrome in one generation of an Italian family where three siblings were affected [Table 1].

Here we describe a two-generation family with Brown syndrome suggestive of dominant inheritance where, unlike previous reports, consistent laterality of the condition (in this case the left eye) was seen in all affected members.

Case Reports

Case 1

The proband, a six and a half-year-old girl, [Figure 1] presented with the parental observation of poor elevation of her left eye towards her nose from infancy. Her mother had also been diagnosed as having Brown syndrome in her childhood, for which a strabismus surgery had been performed when she was one year old. On examination, the child had a visual acuity of 20/40 in the right eye and 20/30 in the left eye with a stereo acuity of 500 seconds of arc. Stereo acuity was tested at near using the Titmus test (Stereo Optical, Chicago, IL) as per the manufacturer's instructions. Her ocular motility showed limited dextro-elevation of the left eye with down shoot on adduction. She was orthotropic for distance and near [Figure 2]. The remainder of her ocular examination was normal. A clinical diagnosis of Brown syndrome was made. An annual orthoptic follow-up was recommended with the advice that no treatment was required unless the child was symptomatic with a deviation in the primary position or on down gaze. Given the positive family history of Brown syndrome a clinical examination of the siblings and mother was carried out.

Case 2

This was the four and a half-year-old younger sister of the proband [Figure 1]. On examination, the visual acuity was

Table 1: Reported cases of familial Brown syndrome and the present report

Report	Affected Individuals	Gender	Laterality
Gowan[2]	Two siblings	M & F	Unilateral/right and left
	Mother, sister, son & daughter		Unilateral/right and left
Moore[3]	Two siblings	M & F	Bilateral
Hamed[4]	Three siblings	2 M & 1F	Bilateral
Iannacone[5]	Three siblings	2F & 1M	Unilateral/left
Katz[6]	Monozygotic twins	F	Unilateral/right and left
Finlay[7]	Monozygotic twins	F	Unilateral/right and left
Magli[8]	Mother & daughter		Unilateral/right
	Father & son		Unilateral/right and left
	Dizygotic twins	M	Unilateral/left
Brown[9]	Aunt & nephew		Unknown
	Mother & daughter		Unknown
Our report	Mother & two daughters		Unilateral/left

M = male, F = female

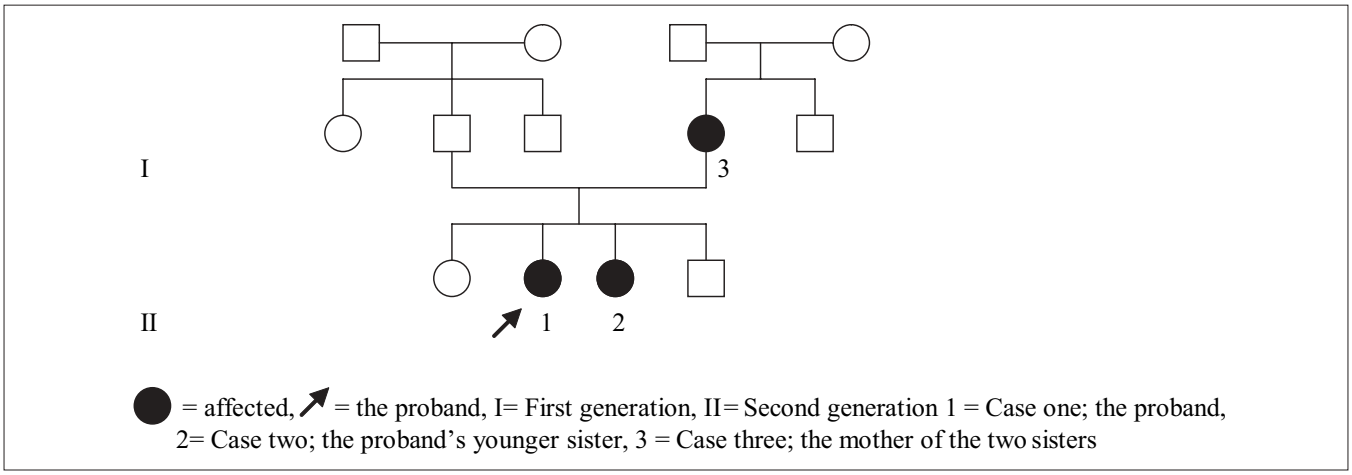

Figure 1: Family tree

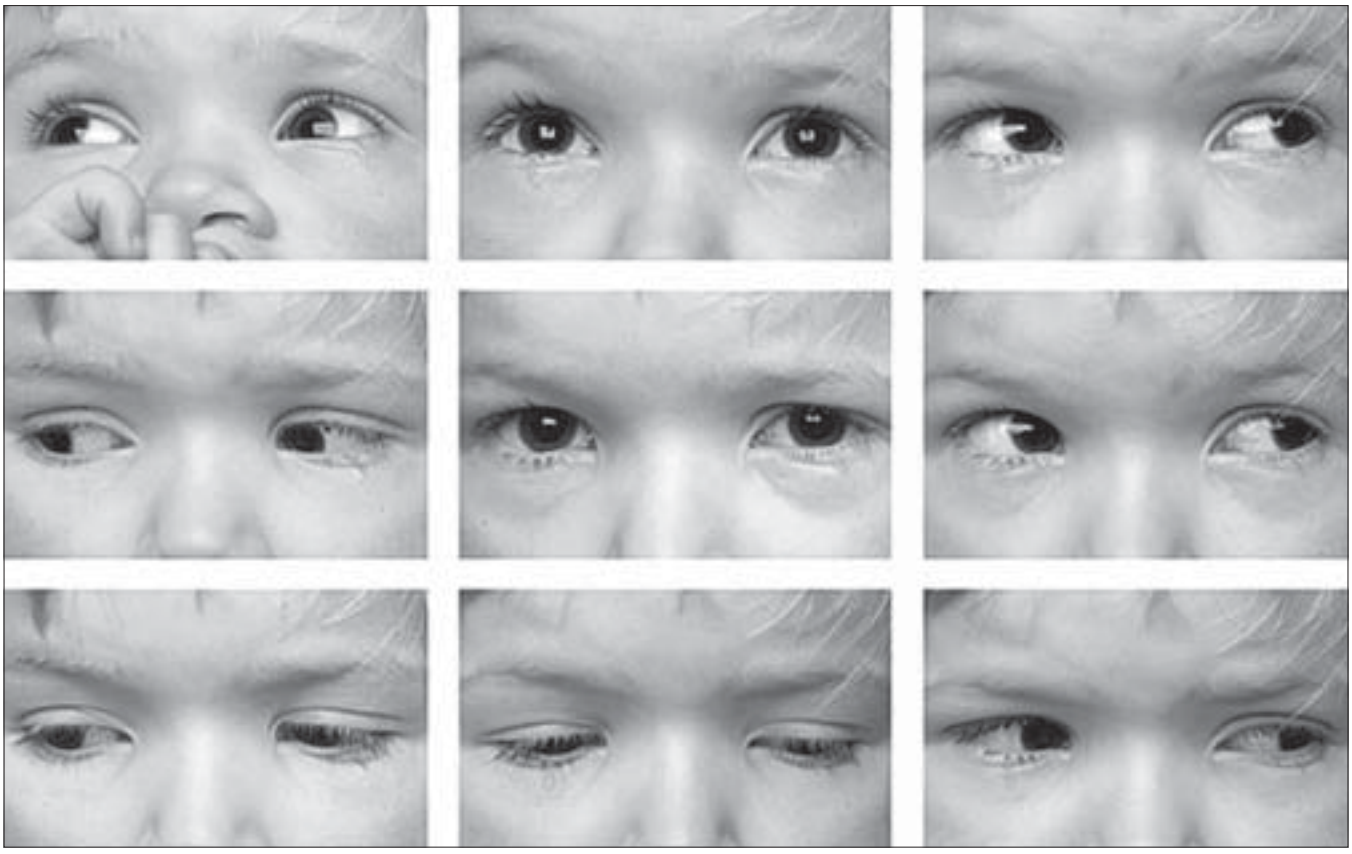

Figure 2: The proband in nine positions of gaze

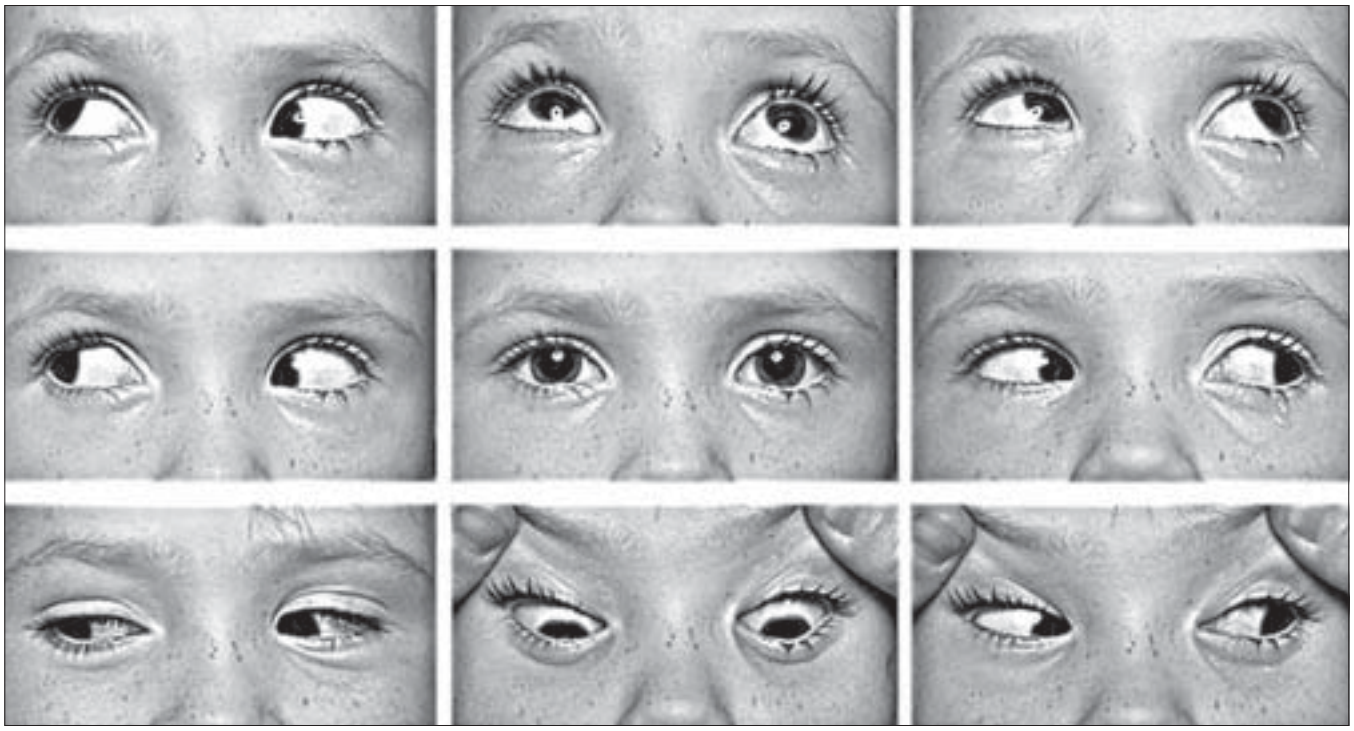

Figure 3: Case 2, younger sister of the proband

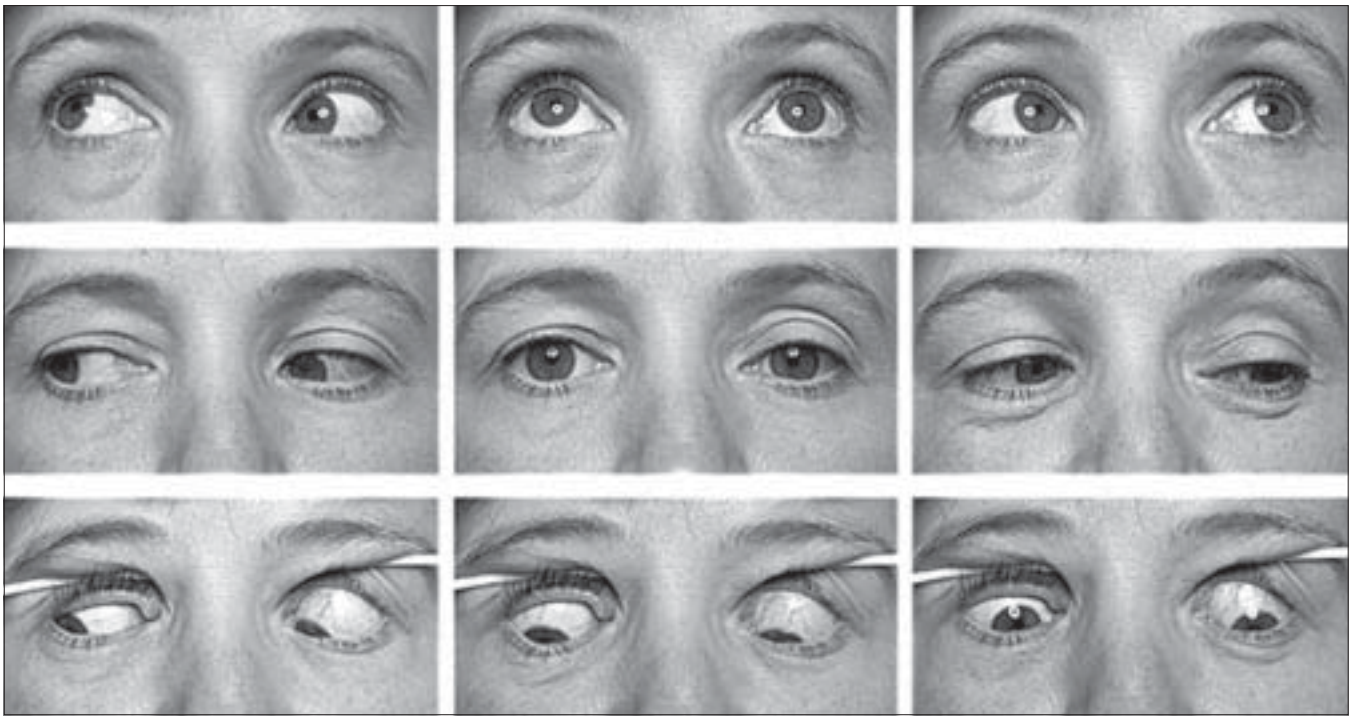

Figure 4: Case 3, mother of the proband

20/20 bilaterally with a stereo acuity of 100 seconds of arc using the Titmus stereo acuity test. Her ocular motility examination revealed a limitation of dextro-elevation of the left eye [Figure 3]. The cover test showed 2 diopters of exophoria for distance and 4 diopters of exophoria for near. Her ocular examination was otherwise normal. A diagnosis of familial Brown syndrome was made and this patient, akin to her sister mentioned above was recommended an annual orthoptic review. No surgical treatment was required.

Case 3

Review of the records showed that the 41-year-old lady, who was the mother of the above children (the proband and her sibling) [Figure 1] had been diagnosed as having a left eye superior oblique tendon sheath syndrome. A left superior oblique partial tenotomy procedure had been performed at one year of age. Her ocular motility examination showed persistent limited elevation on adduction of the left eye [Figure 4] consistent with a diagnosis of a left Brown syndrome. As she was asymptomatic and her visual axes parallel in the primary position and in down gaze, no further treatment or follow-up was advised.

The proband's eldest sister, who was12 years old, and youngest brother, who was one year old, were examined and did not show any extraocular motility abnormality [Figure 1]. Yearly review of the brother has been recommended. The father was not available for examination but he was not known to have any extraocular motility abnormalities. Neither of the parents had any relevant family history of significance.

Discussion

The mother and her two daughters described here presented with defective dextro-elevation of the left eye since childhood and their ocular motility examination was consistent with left Brown syndrome. Although the mother had undergone a corrective surgery in childhood, neither of the daughters had any indication for surgical intervention.

The incidence of familial Brown syndrome is believed to be one in 20,000 live births. It equally affects males and females and is bilateral in about 10% of cases.[10] Brown syndrome together with Duane's syndrome and congenital fibrosis of the extraocular muscles (CFEOM) have been classified by Brown as the congenital fibrosis syndromes based on the findings of both active and passive restriction of ocular motility and the congenital non-progressive nature of the condition.[1] Unlike Brown syndrome, genetic studies have shed light on the etiology of both Duane's syndrome and CFEOM. Heterozygous mutations in KIF21A have been reported in CFEOM1 and 3[11] and CFEOM2 has been attributed to mutation in PHOX2A/ARIX gene.[12] While no gene defect has been identified for isolated Duane's syndrome, DURS2 locus on Chromosome 2 has been mapped, and SALL4 and HOXA1 were reported in other associated anomalies.[13]

Iannacone *et al*.,[5] described unilateral Brown syndrome in an Italian family and excluded linkage to the known CFEOM gene ARIX and the FEOM3 locus. An autosomal recessive or an autosomal dominant inheritance with reduced penetrance was postulated.

To our knowledge this is the first report to identify three members of two generations of the same family with ipsilateral left-sided Brown syndrome. Although no genetic workup was carried out, the clinical presentation of the cases in this report is suggestive of possible autosomal dominant transmission.

Conclusion

Our family supports previous literature reports of possible autosomal dominant inheritance in Brown syndrome, and suggests that the phenotype can breed true in terms of laterality. We recommend genetic counseling in all Brown syndrome cases and their families as to the probabilities of inheritance.

Acknowledgments

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