Oculofacialbulbar palsy in mother and son: review of 26 reports of familial transmission within the 'Möbius spectrum of defects'

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Abstract

We report a mother and son with 5th, 6th, 7th, and bulbar cranial nerve paralysis, who had two similarly affected relatives. None of them had primary skeletal defects. Twenty-six previous reports of familial cases within the heterogeneous 'Möbius spectrum of defects' were reviewed. When cranial nerve palsies were associated with a primary skeletal defect, familial transmission was not found. No recurrence was noted in 31 cases with cranial nerve palsies associated with oral abnormalities and limb defects. The term Möbius syndrome should be restricted to cases with congenital 6th and 7th nerve paralysis with skeletal defects, who have a low recurrence risk (2%). The features in an index case which may indicate a higher risk of recurrence are the absence of skeletal defects, isolated facial palsy, deafness, ophthalmoplegia, and digital contractures. A recurrence risk of 25 to 30% in these cases appears reasonable.

The essential clinical features of Möbius syndrome are difficult to define. The original five sporadic cases reported by Möbius¹ were described as having congenital bilateral 6th and 7th nerve palsies. Two cases also had digital contractures, another two had hypoplastic lacrimal punctae, and other features, seen in single cases, included 5th or 12th nerve palsies, bifid uvula, epicanthus, epilepsy, and anosmia.¹ At least 200 cases have subsequently been published. Necropsy

reports suggest at least four pathological explanations for the clinical signs.² These are (1) hypoplasia or absence of central brain stem nuclei, (2) destructive degeneration of the central brain stem nuclei, (3) peripheral nerve involvement, (4) myopathy. These findings suggest that the group as a whole is heterogeneous. It is therefore not surprising that both sporadic and familial cases have been reported, and that the inheritance of the condition has not been clearly elucidated.

We report a family with bilateral 6th and 7th nerve palsies, horizontal gaze palsies, and incomplete bulbar involvement resembling Möbius syndrome. In this paper, the term Möbius syndrome is restricted to sporadic cases with 6th and 7th nerve palsies and primary skeletal defects, such as syndactyly, brachydactyly, or oligodactyly. We discuss previously reported familial cases and clinical signs which may indicate familial transmission in an isolated case.

Case reports

CASE 1

The proband, a male infant, was born at term weighing 3200 g. The pregnancy and delivery were normal. He had difficulty in feeding owing to poor sucking and his weight at 3 months was just below the 3rd centile. At 6 months, he was feeding well and thriving. Neurological examination and head circumference at birth were normal, as was the early psychomotor development. His head control was good at 3 months and he was sitting independently for long periods at 7 months.

Facial appearance

Incomplete bilateral ptosis, an 'expressionless' face, and an abnormal tongue were noted soon after birth. He had a prominent metopic suture, a right lop ear, upward slanting palpebral fissures, and epicanthic folds (fig 1). The tongue was small and narrow with limited protrusion, and the left side was markedly hypoplastic with widespread fasciculation. At the age of 6 months, the marked discrepancy in size between the left and right halves of the tongue was no longer

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Figure 1 Case 1. (A) The tongue is small with pronounced hypoplasia of the left side. (B) At 6 months only mild asymmetry is present. (C) Face at 6 months showing prominent metopic suture, epicanthic folds, right divergent squint, lopped right ear, and 'serious' face despite 'smiling eyes'.

evident and deep longitudinal grooves were seen. The face was asymmetrical and expressionless. The left corner of the mouth was lower than the right and bilateral ptosis was more severe on the right side. The head was tilted back and to the left and the forehead was wrinkled.

Ophthalmic examination

The conjugate vertical movements were full. He had a variable right divergent squint, with a small left hypertropia (left eye position above horizontal). Testing of the horizontal eye movements showed absent abduction and very limited adduction of both eyes. On prism cover test, there was an isotropia for near fixation that varied between 18 and 30 dioptres. The pupillary responses were normal and on fundoscopy normal retinal vessels and discs were present. A gap on gentle lid closure was not seen or reported by the mother. There was a normal Bell's phenomenon; the corneas were healthy with no exposure keratopathy.

Vision testing showed steady normal central fixation and refixation with either eye and tolerance for alternate occlusion. Retinoscopy under cycloplegia showed no refractive error.

General examination

No skeletal malformations or deficiency in brachial muscle groups were present. The clinical systems examination was normal apart from glandular hypoplasias.

CASE 2

The proband's mother had marked congenital facial asymmetry, incomplete ptosis, a furrowed tongue, and abnormal eye movements (fig 2). She also gave a history of congenital hemiplegia, with flaccid paralysis of her left arm, leg, and face, which had improved apparently in the first year of life.

Figure 2 Case 2, mother of case 1. (A) Asymmetrical, expressionless face, epicanthic folds, and divergent squint and (B) hypoplastic tongue.

Facial appearance

The face was 'immobile' and asymmetrical; ptosis and drooping of her mouth were more pronounced on the left side. She could give a weak smile. The perception of light touch and pin prick were diminished on the left lower two thirds of the face. The left side of the tongue was wasted with longitudinal furrows and marked fasciculation was visible. Tongue protrusion was limited and the palate moved sluggishly. Her speech was of nasal quality and occasionally indistinct.

Ophthalmic examination

The abnormality of the eye movements was very similar to that of her son. The vertical eye movements were normal; there was bilaterally absent abduction and reduced adduction, especially on the left side. On attempted adduction of the left eye there was narrowing of the palpebral fissure and downdrift of the left eye. A constant, small amplitude, high frequency, left rotatory nystagmus was present in all positions of gaze. She had normal pupillary responses and fundoscopy. Corrected acuities were 6/9 in either eye.

General examination

No skeletal malformations or deficiency in brachial

muscle groups were present. The clinical systems examination was normal. Careful neurological assessment in view of her birth history was performed, but tone, muscle power, and muscle mass were equal on both sides. The gait was normal. Reflexes were symmetrical and equal with no clonus and both plantar reflexes were flexor. The intelligence was not formally tested, but was considered to be normal. Chromosome analysis showed a normal 46,XX karyotype.

Family history

According to the mother, her maternal aunt and her

Figure 3 Family pedigree of III·4 (case 1) and II·6 (case 2) with bilateral 6th, 7th, and bulbar palsy. I·1 and II·1 are apparently similarly affected relatives.

son (fig 3) had asymmetrical faces from birth, abnormal eye movements, and furrowed tongues, with normal intelligence and no skeletal malformations. We were not able to examine these apparently affected relatives.

Discussion

The clinical signs in previous cases reported as 'Möbius syndrome, Möbius variant, or Möbius-like syndrome' include variable cranial nerve and gaze palsies, facial and auricular abnormalities, peripheral joint contractures, and primary musculoskeletal defects of the facial-limb disruptive spectrum, such as phocomelia, oligodactyly, and brachydactyly.² As indicated by different pathology found at necropsies, these cases are heterogeneous. Familial transmission is frequently cited in published reports. It has been suggested that if the definition of Möbius syndrome is restricted to the presence of 6th and 7th nerve palsies with or without bulbar involvement with primary skeletal defects, a clinical entity with low (2%) recurrence risk can be defined.³ We have reviewed 26 reports of 'familial Möbius syndrome' to see whether there is clinical overlap with 'low recurrence risk' Möbius syndrome as defined above.

A number of features which would aid the recognition of familial cases were found, and one previously reported pedigree resembled the family reported here.

The two documented cases in our family presented with asymmetrical bilateral incomplete facial palsy, bilateral loss of abduction of the eye with incomplete adduction, a gaze palsy with some features of Duane syndrome in the mother, tongue wasting and fasciculation, and difficulty in swallowing and phonation. The presence of a horizontal gaze palsy and Duane syndrome in the mother probably represents no more than a lesion of different size and specificity from that of her son. This postulated lesion would involve either gaze neurones, abducens neurones, or both in the pontine horizontal gaze centres, which are intermingled with the 6th nerve fibres.⁴ Our two cases had no congenital skeletal or peripheral muscle defects. Intelligence was normal in the mother (case 2) and her son (case 1) had normal psychomotor development at 6 months. The pedigree (fig 3) contained two additional cases with apparently identical clinical signs, which we were unable to examine. Autosomal dominant inheritance with incomplete penetrance is likely, but no male to male transmission was observed.

From previously described familial cases (tables 1 to 5) only family 23 reported by Legum *et al*¹⁸ appears similar (table 4). This pedigree contains 10 cases with 6th and 7th nerve palsy, seven of whom also had paralysis of the 3rd and 4th cranial nerves (external ophthalmoplegia), and three of these seven had additional bulbar palsy. Neither musculoskeletal

abnormalities nor mental retardation were reported. Hypoplastic teeth were seen in a 32 year old male and a small tongue in his 18 month old son. Autosomal dominant transmission and lack of mental retardation or musculoskeletal defects would place this pedigree and our cases into the group of families with multiple cranial nerve involvement (table 4).

External ophthalmoplegia was present in seven cases from pedigree 23 (table 4).¹⁸ Families with congenital, non-progressive, external ophthalmoplegia have been described, and the entity of 'ophthalmoplegia plus' contains a high proportion of cases with progressive mitochondrial disease. It can be concluded that a high recurrence risk is likely for an isolated case with external ophthalmoplegia with or without other cranial nerve palsies. The familial published cases and the family reported here can be divided into five groups based on clinical signs.

GROUP 1: CONGENITAL FACIAL NERVE PALSY (TABLE 1, FAMILIES 1-9)

This is the most frequently reported, apparently isolated cranial nerve palsy with autosomal dominant transmission. As some congenital myopathies may present with congenital facial palsy, this finding alone, if bilateral, might constitute a high risk group. The two sibs of Harrison and Parker¹² might be different as both were mentally handicapped. Without the 6th nerve palsy and skeletal defects, this group does not fulfil the criteria for Möbius syndrome. Sib risks are probably small, but caution should be exercised in counselling the risk for offspring.

GROUP 2: 6TH TO 8TH CRANIAL NERVE PALSY (TABLE 2)

Affected subjects in these families show no consistent pattern of cranial nerve involvement. Familial transmission of isolated 6th and 7th nerve palsies was not seen. In two families, transmission of 6th and 7th nerve palsies occurred, but with additional clinical signs. These were puberty onset of neurogenic deafness in a sib pair¹⁶ and one case with mental retardation, neurogenic deafness, webbing of fingers, and a supernumerary thumb.¹⁹ Affected subjects from families 10 and 13 had 7th and 8th nerve palsies, as had the proband from family 12. Associated skull and ear malformations (families 12 and 14) and conductive hearing loss (family 11) indicate different causes of cranial nerve palsies and are likely to be separate clinical entities. This group is heterogeneous, but deafness should separate these cases from those with Möbius syndrome. Structural ear abnormalities were present in one sib pair (family 10) and deep set eyes with narrow palpebral fissures in one case (family 17). Isolated talipes and phocomelia were reported in two relatives of the proband from family 10.

Table 1 Group 1: congenital facial nerve palsy (families 1–9).

Family no () and reference	Family	Cranial nerves				Abnormalities				Pedigree
		VI	VII	VIII	IX–XII	MR	Neuro	Limbs	Other	
(1) 5	6 generations, 14 affected, parents had 32/70 affected offspring	–	+ or UN	–	–	–	–	–	–	AD, incomplete penetrance (pedigree not given)
(2) 6	4 generations, 16/50 affected	–	UN (one pt+)	–	–	–	Ptosis (UN) Ptosis	–	–	AD, no male male to male transmission
(3) 7	40/117 affected	–	UN	–	–	–	–	–	–	AD (pedigree not given)
(4) 8	3 generations, 18/31 affected	–	+ or UN	–	–	–	–	–	Necropsy 3 cases partial agenesis of facial motor nucleus	AD, incomplete penetrance
(5) 9	3 generations, 3 affected parents had 5/13 affected offspring	–	+	–	–	–	–	–	–	AD
(6) 10	Father Son	–	+	–	–	–	–	–	Low set, cupped ears	AD
(7) 11	Daughter Sister Brother	–	+	–	–	–	–	–	–	–
(8) 12	Male Male (mat 1st cousin) Male	–	UN UN + + +	–	– – UN XII –	– – + + –	– – – – –	– – – – –	– – – – –	? X linked ? AR parents 1st cousins No FH
(9) 3	Male Brother	–	+	–	+	–	–	–	–	–

UN=unilateral, + (cranial nerves)=(bilateral paralysis, + (abnormalities)=present, – absent.

Table 2 Group 2: 6th to 8th cranial nerve palsy (families 10 to 17).

Family no () and reference	Family	Cranial nerves					Abnormalities				Branchial muscles	Other	Pedigree
		VI	VII	VIII	IX-XII	MR	Neuro	Skeletal	Ear				
(10) 13	Male	-	+	+	-	-	-	-	-	-	Cleft earlobes, lop ears	Cleft earlobes, lop ears lop ears ?	?
	Brother	-	+	+	-	-	-	-	-	-			
	Sib (neonatal death)	?	?	?	?	?	?	Deformed foot					
	Mat 1st cousin	-	-	-	-	-	-	Phocomelia UL					
(11) 11	3 generations 9 cases	-	+	-	-	-	-	Hypertrophy of maxilla, hyper- telorism		-	Congenital conductive hearing loss		?AD (pedigree not given)
(12) 14	11 cases	-	+	-	-	-	-	Mild skull malformation "		-	Absent lachrymation		?AD
	7 cases	-	-	+	-	-	-			-			
(13) 15	Female	-	UN	UN	-	-	-			-			AD, incomplete penetrance
	Brother	-	+	+	-	-	-			-			
	Mat cousin	-	+	+	-	-	-			-			
	8 cases	-	+	-	-	-	-			-			
	3 cases (in 4 generations)	-	-	+	-	-	-			-			
(14) 16	3 cases	-	(UN)	+	-	-	-	Facial canal hypoplasia, 2 cases	+	Lop ears, microtia, 1 case	Aplasia cutis congenita of the scalp, dermal sinus		AD
	4 cases	-	-	-	-	-	-			-			
(15) 17	Female	-	+	+	-	-	-			-			?AR, parents cousins
	Sister	+	+	-	-	-	-			-			?AR, 1st cousin parents
(16) 18	Male	+	+	+	-	-	-			-			
	Sister	+	+	+	-	-	-			-			
	(at puberty)												
	(at puberty)												
(17) 19	Male	+	+	+	-	+	-	Webbed fingers, supernumerary thumb		-			
	Mother	+	+	-	-	-	-			-		Deep set eyes, narrow palpebral fissures	

Table 3 Group 3: familial muscle aplasia and skeletal defects in relatives (families 18 to 22).

Family no () and reference	Family	Cranial nerves					Abnormalities					Pedigree
		VI	VII	VIII	IX-XII	MR	Neuro	Skeletal	Ear	Branchial	Other	
(18) 20	Male	+	-	-	-	+	Prosis	-	+	Bilateral scapular defects	-	Consanguinity (Black Forest isolate)
	Sister	+	-	-	-	-	-	-	+	-	-	
	Sister	-	-	-	-	-	-	CDH	+	Pectoralis defect	-	
(19) 21	Female	+	-	-	-	-	Prosis (UN)	Talipes (UN)	-	-	-	
	Father	-	-	-	-	-	-	Phocomelia (UN)	-	-	-	
(20) 22	Female	-	-	-	-	-	-	Oligo-syndactyly (UN)	-	-	-	
	Sister	+	-	+	-	-	-	-	-	-	-	
	Mother	-	?	-	-	-	-	Facial muscle polyphasic EMG	-	-	-	
(21) 23	Male	+	+	?	-	-	Facial muscle, no response on EMG	Bilateral talipes	-	-	-	
	3 cases	-	+	-	-	-	-	-	-	-	-	
	8 cases	-	+	-	-	-	-	-	-	-	-	Mother's family
	4 cases	-	+	-	-	-	-	-	-	-	-	
	6 cases	-	-	-	-	-	-	-	-	-	-	Father's family
	Pat grandfather, his mother and sister, his nephew	-	-	-	-	-	-	Digital contractures	-	-	-	Complete anhidrosis
(22) 24	Male	-	-	-	-	-	-	Talipes	-	-	-	
	Brother	+	+	+	-	+	-	Brachycephaly	-	-	-	
	Brother	-	-	+	-	+	-	Brachycephaly	-	-	-	
	Brother (neonatal death)	-	-	+	-	?	-	Brachycephaly ?	-	-	-	
	Mother's 2nd cousin and another	-	-	-	-	-	-	Cervical myelomeningocele, congenital torticollis	-	-	-	Mother's family
	Father's 3 sibs	-	+	-	-	-	-	-	-	-	-	Father's family

CDH=congenital dislocation of the hip.

Table 4 Group 4: multiple cranial nerve palsy (families 23 and 24).

Family no () and reference	Family	Cranial nerves												Abnormalities				Pedigree
		III	IV	V	VI	VII	VIII	IX	X	XI	XII	MR	Neuro	Skeletal	Ear	Branchial	Other	
(23) 18	Family 1, male (III-5)	+	+	+	+	+	-	+	+	+	-	-	-	-	-	-	Hypo- plastic teeth Small tongue	AD
	Son (IV-4)	+	+	+	+	+	-	-	-	-	+	-	-	-	-	-	-	
	Sister (III-2)	+	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	
	Brother (III-6)	-	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	
	Mat cousin (III-8)	+	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	
	Mat cousin (III-9)	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	
	Mat cousin (III-10)	+	+	+	+	+	-	-	+	-	-	-	-	-	-	-	-	
	Mother (II-1)	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	
	Uncle (II-2)	+	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	
	Aunt (II-3)	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	
(24) This report	Mother	-	+	+	+	+	-	+	+	+	-	-	Prosis	-	-	-	-	? AD, incomplete penetrance
	Son	-	-	+	+	+	-	?	-	-	+	-	Prosis	-	-	-	-	
	Mat aunt (by history)	-	-	+	+	+	-	-	-	-	+	-	-	-	-	-	-	
	Mat cousin (by history)	-	-	+	+	+	-	-	-	-	+	-	-	-	-	-	-	

Table 5 Group 5: cranial nerve(s) palsy and neuromuscular disorder (families 25 to 27).

Family No and reference	Family	Cranial nerves					Abnormalities				Pedigree
		VI	VII	VIII	IX-XII	MR	Neuro	Skeletal	Other		
25) 25	Male	-	+	(UN)	-	+	Prosis	Campodactyly, talipes, pectus excavatum	Nerve conduction-N, t(1p34;13q13)	AD (no male to male trans- mission) Normal karyotype in unaffected sister and her 5 normal children	
	Mother	-	+	-	-	-	Prosis	Campodactyly (3rd + 4th + 5th fingers)	CK-N		
	5 maternal 1st + 2nd degree relatives	-	+	-	-	-	Prosis	Campodactyly (3rd + 4th + 5th fingers)	t(1p34;13q13)		
									t(1p34;13q13)		
26) 26	6 cases	+	+	-	-	-	-	Digital contractures, club feet	-	AD, incomplete penetrance	
	9 cases	-	-	-	-	-	-	Digital contractures	-		
	1 case	-	+	-	-	-	Progressive neuro- muscular weakness	-	-		
27) 3	Male	(UN)	+	-	+	-	Progressive muscular weakness	Talipes	-	Myopathic EMG	
	Sister	-	+	-	-	-	Progressive muscular weakness	-	-		

GROUP 3: FAMILIAL MUSCLE APLASIA AND SKELETAL DEFECTS IN RELATIVES (TABLE 3, FAMILIES 18 TO 22)

Variable brachial muscle defects and inconsistent involvement of the 6th nerve were reported in three sibs (family 18). None of the index cases in families 19 to 21 had Möbius syndrome as defined here. Relatives of these cases had only primary skeletal defects (families 19 and 20) or variable cranial nerve palsies or digital contractures or deafness (family 21). This does not constitute familial Möbius syndrome, but the significance and frequency of these findings in relatives of index cases needs to be elucidated. Family 22 might be different as four male sibs had laryngeal paralysis and mental retardation.

GROUP 4: MULTIPLE CRANIAL NERVE PALSY (TABLE 4, FAMILIES 23 AND 24)

Cases from this report (family 24) and one other family (family 23) have already been discussed.

GROUP 5: VARIABLE CRANIAL NERVE(S) PALSY AND NEUROMUSCULAR DISORDER (TABLE 5, FAMILIES 25 TO 27)

Affected subjects in two families (families 26 and 27) presented with variable 6th, 7th, and bulbar palsy, digital contractures, talipes, and progressive muscle weakness. In a third family (family 25), facial palsy and digital contractures were present in seven subjects with an apparently balanced chromosome translocation (1p34;13q13); the other six were not affected and had a normal karyotype. The affected subjects had no 6th nerve palsy and unilateral deafness was present in one case. No muscle weakness was reported in the affected cases, including the oldest, a 61 year old female. The possibility of late onset of neuromuscular problems cannot be excluded in the latter family and digital contractures should be used as an indication to perform further diagnostic tests.

The main findings from this review of familial cases are the low incidence of mental retardation, 3% (five out of approximately 262 cases), and the absence of primary skeletal malformations. No recurrence was noted by Herrmann *et al*²⁷ in the families of 31 cases with variable cranial nerve palsies associated with oral abnormalities and primary skeletal defects. It can be concluded that primary skeletal defects and isolated 6th and 7th nerve palsies suggest the diagnosis of low recurrence risk (2%) Möbius syndrome.

The clinical findings in subjects from previously published pedigrees with a Möbius spectrum of defects are summarised in the tables. Newly diagnosed cases can be compared to those showing familial transmission and an assessment made about their recurrence risk.

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