Microcephaly, microphthalmia, congenital cataract, optic atrophy, short stature, hypotonia, severe psychomotor retardation, and cerebral malformations: a second family with micro syndrome or a new syndrome?

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Abstract
We report on four children of both sexes from a highly inbred family with hypotonia, spastic diplegia, microcephaly, microphthalmia, congenital cataract, optic atrophy, ptosis, kyphoscoliosis, short stature, severe mental retardation, and cerebral malformations. Six other children may also have been affected. The differential diagnosis and the possibility of a second family with the micro syndrome are discussed.
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Nearly 150 conditions that feature microphthalmia have been delineated.[1] Few of these syndromes have cataract and mental retardation in addition. Here, we describe four children with hypotonia, microcephaly, microphthalmia, congenital cataract, optic atrophy, ptosis, short stature, severe mental retardation, and cerebral malformations. This phenotype is similar to other reported rare entities and especially to a family reported by Warburg *et al*[2] as the micro syndrome. However, these patients may also have a hitherto unreported autosomal recessive malformation syndrome.

This kindred (fig 1) resides in southern Lebanon and belongs to the Shiite Muslim community.

Case 1 (VI.6, fig 1) is the proband. When she was born, the father was 34 and the mother 24 years old. The pregnancy was unremarkable and the baby was delivered by cephalic presentation at 40 weeks when bilateral microphthalmia and cataract were noted. Birth weight was 3300 g (60th centile) and length 51 cm (75th centile). CT scan of the brain was performed at 3½ years and showed signs of cerebral atrophy.

We first examined her at the age of 9 years. She was hypotonic, unable to hold up her head, sit, speak, or react normally to simple orders. Her weight was 15 kg, length 112 cm, and occipitofrontal circumference (OFC) 46.7 cm (all below the 3rd centile). She had bilateral microphthalmia, bilateral ptosis, a long philtrum, a high arched palate, a pointed chin,

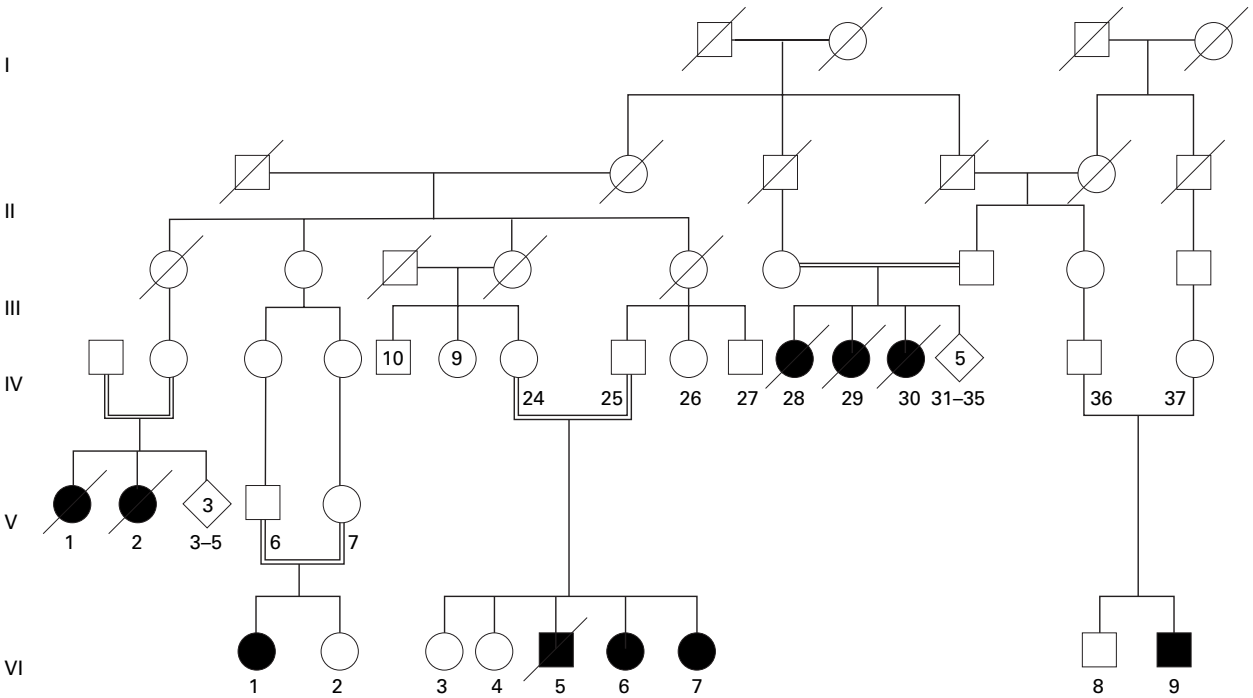

Figure 1 Pedigree of the family.

kyphoscoliosis, contracture at the knees, and flexion contraction of all the fingers, which had developed gradually (fig 2). Her neurological examination showed central hypotonia, spastic diplegia, increased osteotendinous reflexes with crossed adductors, scissoring, poor fixation and following with each eye, with wandering eye movements and horizontal nystagmus. She had no seizures. Her fundus could not be visualised because of undilatable pupils.

Radiological examination of the skeleton showed a left curved scoliosis, convex vertebral bodies, diffuse osseous demineralisation, thin diaphyses of the long bones, bilateral subluxation of the femoral head, and fixed flexion of the knees. The abdominal ultrasound, the echocardiography, and the auditory brainstem responses were normal. Complete blood count, haemoglobin electrophoresis, serum electrolytes, blood glucose levels, triglycerides, cholesterol, amino acid studies of plasma and urine, urine analysis, thyroid, liver, and renal function tests, plasma very long chain fatty acids, and white blood cells enzyme assays were all unremarkable. Chromosomes (high resolution G and R banding) were normal 46,XX.

Case 2 (VI.7, fig 1) was born five years after her affected sister. Except for oligohydramnios, the pregnancy and delivery by cephalic presentation at 40 weeks were unremarkable. Birth weight was 3280 g (60th centile) and length 50 cm (60th centile). At 4 years, her weight was 12 kg, length 101 cm, and OFC 46.8 cm (all well below the 3rd centile). Her clinical history and physical appearance were quite similar to those of her affected sister (fig 3), except that she did not have contractures of the extremities and had a mild kyphoscoliosis to the right. The pupils were sluggishly reactive to light. Portable slit lamp evaluation showed a clear cornea of 8 mm diameter in both eyes (normal average value 11.8 mm) and slightly shallow anterior chambers. There were dense mature cataracts in both eyes with no view of the fundus. A and B scan ultrasonography showed globes of 19 mm axial length. No retinal detachment or mass lesion were detected in the posterior segments. Visual evoked potentials and electroretinogram disclosed the presence of bilateral optic atrophy.

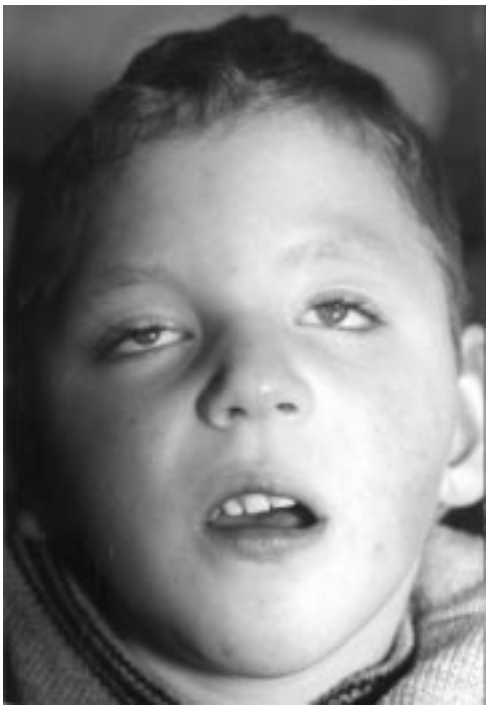

Figure 3 Facial appearance of case 2 showing the general hypotonic aspect and the bilateral microphthalmia.

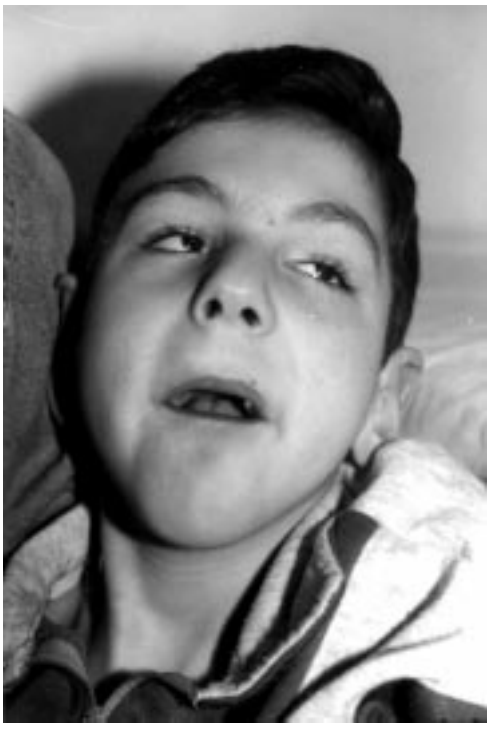

Figure 2 Facial appearance of case 1 at the age of 9 years. Note the bilateral microphthalmia and ptosis, the long philtrum, and the pointed chin. (Photographs reproduced with permission.)

MRI of the brain showed plagiocephaly, moderate subcortical atrophy with hypoplasia of the corpus callosum predominantly posteriorly, and hypotrophy of the white matter of the centrum semiovale. It also showed gyration anomalies mainly in the medial-frontal region (fig 4). The cerebellum and the brain stem were normal. Electroencephalography (EEG) was unremarkable. As in case 1, radiological examination of the skeleton showed subluxation of P2 over P1 of the left big toe. Bone age was 4 years. All other laboratory and radiological findings were identical to those of her affected sister. Chromosomes were normal 46,XX on G and R banding.

Results of the ophthalmological and physical examinations of the parents and their other children were completely normal, apart from one boy (VI.5, fig 1) who had the same problems as his affected sisters. A CT scan performed at 16 months showed cerebral atrophy in the right frontoparietal region with an increased density of the surface of the brain. He died at the age of 5 years from an unknown cause.

Case 3 (VI.1, fig 1) had a birth weight of 3100 g (40th centile), length 49 cm (50th centile), and OFC 32 cm (<3rd centile). At the

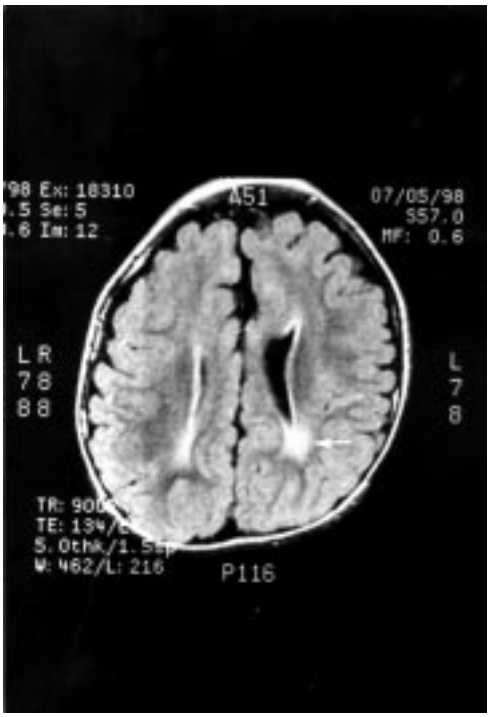

Figure 4 MRI of the brain of case 2 showing plagiocephaly, gyration anomalies, and abnormal white signal (arrow).

time of examination she was 18 months old. Her weight was 9.30 kg (5th centile), length 76 cm (5th centile), and OFC 43.2 cm (<3rd centile). She had a single palmar crease on the right hand like her affected cousins. MRI was not performed.

Case 4 (VI.9, fig 1) was delivered at 39 weeks of gestation with a birth weight of 2600 g (15th centile), a length of 48 cm (50th centile), and an OFC of 31.5 cm (<3rd centile). The pregnancy was unremarkable, but the mother noticed that fetal movements were decreased compared to her other child. At the age of 13 months, he weighed 9.7 kg (25th centile), had a length of 76 cm (35th centile), and an OFC of 42.8 cm (<3rd centile). His clinical course was identical to that of the other affected members of the family. He had undescended testes. MRI scan of the brain showed diffuse cortical and subcortical atrophy, hypoplasia of the corpus callosum predominantly posteriorly, and diffusely abnormal signal of the subcortical white matter with reduced myelination, bilateral hippocampic malformation, and small orbits (fig 5). All other investigations, including *x* rays, were normal.

Five other children in this family were also thought to be affected (IV.28-30, V.1, 2, fig 1). According to their parents and to hospital notes, all had micophthalmia and cataract and never walked or talked. Case IV.28, a girl, also had a bilateral simian crease and a pneumoencephalogram at the age of 18 months that showed brain atrophy and atrophy of the brain stem. She died at 7 years. No other data are available. Cases V.1 and V.2 died at 11 years and 15 years respectively.

The four children reported here, and most probably six others, share the following clinical characteristics: hypotonia, microcephaly, congenital microphthalmia and cataract, ptosis, short stature, severe psychomotor retardation, and cerebral malformations. Some of these features overlap those of a number of rare conditions.

The Lenz microphthalmia syndrome (MIM 309800) and the entities reported by Bavink *et al*,[3] Seemanova and Lesny,[4] and Siber[5] have many manifestations which overlap the condition reported here. However, all of these have an X linked mode of inheritance which helps to differentiate them from our family. The cerebro-oculo-facio-skeletal (COFS) syndrome (MIM 214150), the CAMAK/CAMFAK syndromes, and Cockayne syndrome (MIM 216400) are ruled out as well because of their different phenotype (table 1). Also, RNA recovery synthesis performed on case 2 was normal, which eliminates Cockayne syndrome. The family reported by Tomiwa *et al*[6] had short stature, microcephaly, cataract, hypotonia, spasticity, and mental retardation. However, other features, like deafness and seizures, were absent in our sibs, with evident microphthalmia (table 1). Martsolf syndrome consists of the presence of short stature, microcephaly, high arched palate, scoliosis, hypogonadism, mental retardation, hirsutism, and malformations of the hands.[7] Our sibs did not have the last two features, but they had microphthalmia, severe mental retardation, and congenital cataract (table 1).

Mégarbané *et al*[8] reported on a highly consanguineous family where two boys, cousins, presented facial dysmorphism, microcephaly, colobomatous microphthalmia, skeletal malformations, psychomotor retardation,

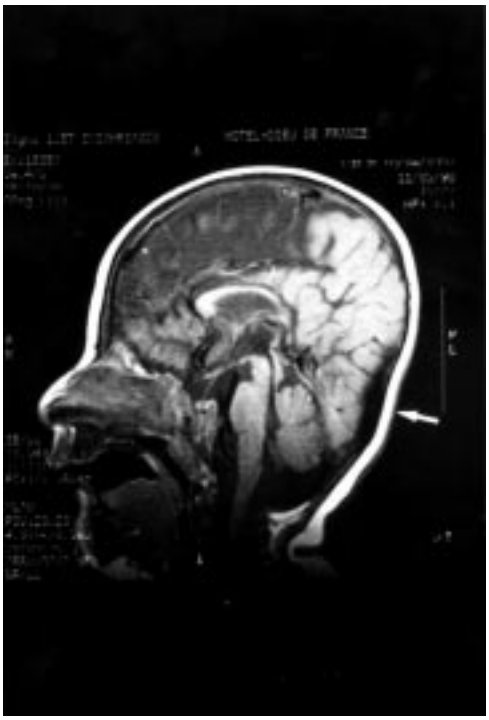

Figure 5 MRI of the brain of case 4 showing diffuse cortical and subcortical atrophy, hypoplasia of the corpus callosum (small arrow), and abnormal occipital region (large arrow).

Table 1 Clinical comparison between our patients and other similar syndromes

	Present report	*COFS*	*CAMFAK*	*Tomiwa et al*[6]	*Martsolf et al*[7]	*Mégarbané et al*[8]	*Warburg et al*[2]
Severe growth retardation	+	+	+	+	-	+	-
Spasticity	+	-	-	+	-	-	+
Hypotonia	+	+	+	+	+	+	+
Never walked	+	-	+,-	-	-	+	-
Mental retardation	+	+	+	+	+	+	+
Short stature	+	-	-	+	+	+	+
Congenital microcephaly	+	+	+	-	+	+	+
Microphthalmia	+	+	+	-	-	+	+
Congenital cataract	+	+	+	+	-	-	+
Coloboma	-	-	-	-	-	+	-
Optic atrophy	+	-	-	-	-	-	+
Ptosis of eyelids	+	-	-	-	-	-	-
Large ears	-	+	+	-	-	-	+
Abnormal nasal tip/bridge	-	+	+	-	+	-	+
High arched palate	+	-	-	-	+	+	-
Kyphosis	+	-	-	-	-	-	+
Scoliosis	+	-	-	-	+	-	-
Joint laxity	-	-	-	-	+	-	-
Cryptorchidism	+	-	+	-	+	+	+
Dermatoglyphic abn	+	-	-	-	+	+	-
Incurved 5th fingers	+	-	-	-	-	+	-
Ag/hypoplasia of the CC	-/+	+/+	+/+	-/-	-/-	-/-	+/-
Osseous malformations	+,-	-	+	-	-	+	-
Deafness	-	+,-	-	+	-	-	-
Seizures	-	-	-	+	+	+	-

Ag = agenesis, CC = corpus callosum.

and short stature. This family originated from the south of Lebanon, 40 km from the families under study, and is from the same religious community. Nevertheless, their different phenotype, the presence of coloboma and radiographic abnormalities and the absence of congenital cataract, and severe psychomotor retardation help to differentiate them clinically from the present patients (table 1).

Another rare condition that could be considered in the differential diagnosis is that of the family reported by Warburg *et al*[2] as the micro syndrome. Both families have in common microcephaly, microphthalmia, congenital cataracts, optic nerve atrophy, abnormal corpus callosum, cryptorchidism, and mental retardation (table 1). The absence of hypertrichosis in the present report could be explained by ethnic factors. The presence of ptosis of the eyelids and osseous abnormalities might also be related to the affectedness of the central nervous system. Although the cases of Warburg *et al*[2] had agenesis of the corpus callosum rather than hypoplasia as reported in cases 2 and 4 of the present family, one of them also had lissencephaly, which would constitute a gyral abnormality as reported here in case 2. Unfortunately, MRI was not performed on the family of Warburg *et al*[2] for further comparison. However, our patients do not have the minor facial anomalies reported in that family and have high arched palate, severe growth and psychomotor retardation with inability to walk or speak, and early death for some (table 1). Thus, our family could have another close or allelic entity to the micro syndrome. The localisation of the relevant gene will help in better understanding the origin of these similar autosomal recessive entities.

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