A genetic syndrome that mimics congenital TORCH infection

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Abstract

Warburg micro syndrome (WARBM) or Micro syndrome is a rare, genetically heterogeneous, autosomal recessive syndrome. Patients with WARBM present with severe mental retardation, brain anomalies (polymicrogyria and corpus callosum hypoplasia), craniofacial features (microcephaly, hairy forehead, large anteverted ear, broad nasal root and micrognathia), ocular defects (congenital cataract, microphthalmia and microcornea), spasticity leading to contractures, congenital hypotonia and hypogonadism. Here we report three cases of Micro syndrome from two different families. All cases had congenital cataract and were born to consanguineous parents. Hypoplastic genitalia was present in cases 2 and 3 (sibs), whereas absent in case 1. Mutation analysis of the *RAB3GAP1* gene showed a nonsense mutation in exon 3 in case 1 and in exon 13 in cases 2 and 3 (sibs). Case 3, the sib of case 2, was diagnosed antenatally-initially level II antenatal ultrasound at 19 weeks gestation showed evidence of fetal cataract and further mutation analysis confirmed the affected status of the fetus. About 144 cases of Micro syndrome have been described till date world-wide in literature. These cases are the first case series of Micro syndrome from India. Our cases had all the classical clinical features described in literature, with an exception being the absence of genital abnormalities in case 1. Prominent incisors were present in both cases 1 and 2, which has not been reported earlier. Prenatal diagnosis of fetal cataract in Micro syndrome has also not been reported earlier.

Introduction

Warburg Micro Syndrome (WARBM, MIM 600118), also known as Micro Syndrome, is characterized by microcephaly, mental retardation, corpus callosum hypoplasia, diffuse cortical or subcortical atrophy, congenital cataracts, microcornea, microphthalmia, progressive joint contractures with growth failure, and hypothalamic hypogonadism. This syndrome was first described by Warburg et al. in a consanguineous Pakistani family with two affected sibs and an affected male cousin (Warburg et al., 1993).

Patients and Results

Case 1

This male child initially presented at 4.5 years of age with global developmental delay. He had infantile spasms since the age of day 7 and was on antiepileptic drugs for the same. He was born at full term to a third degree consanguineous couple. His birth weight was 2.7 kg and had delayed cry at birth. He was noted to have bilateral cataract at birth. IgM rubella serology was negative.

Examination showed presence of microcephaly

with plagiocephaly, microcornea, long palpebral fissures, prominent incisors and bilateral simian crease (Fig 1). Neurological examination at initial presentation showed presence of spasticity and brisk reflexes. On follow up at 9 years of age, he had central hypotonia. There was no undescended testis or cardiac involvement. There was no spinal deformity. CT scan of the head showed partial fusion of the lambdoid and coronal sutures. MRI of the brain was suggestive of agenesis of corpus callosum. The karyotype was normal. MLPA for subtelomeric deletions was normal. A clinical suspicion of Micro syndrome was made and the child was tested for the same. A homozygous deletion c.129delT (p.Leu44Trpfs*49) in *RAB3GAP1* was identified in the patient in exon 3. This variant is likely to be pathogenic as it results in a frameshift. Both parents were heterozygous for this mutation consistent with the carrier status.

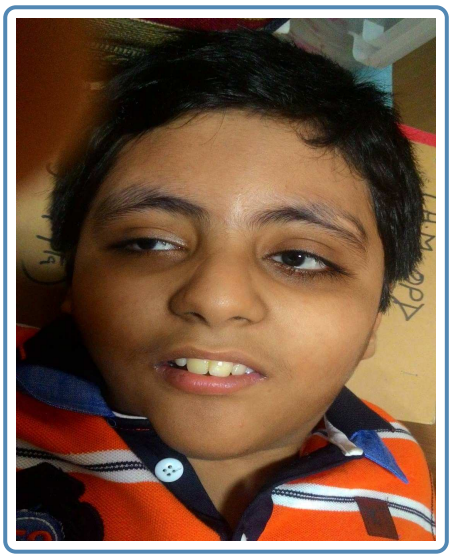


Figure 1 Face of Case 1 showing microcornea, long palpebral fissures, prominent incisors.

Case 2

This 27 years old second gravida was referred to our genetic clinic at 6 weeks for prenatal counselling and diagnosis, as her first child had severe developmental delay.

The proband was a 5 years old boy who had global developmental delay. He had been delivered by Caesarean section at 36 weeks of gestation, in view of leaking and meconium stained liquor. The birth weight was 2.8 kg. The length at birth was 47 cm and head circumference at birth was 32 cm (7th centile). Penile length of 1 cm was documented in the newborn period, suggestive of micropenis. There was no history of birth asphyxia. He was operated for congenital cataract on day 22 of life. His vision did not improve even after cataract surgery. At 5 years of age the child was able to hold his neck but was unable to sit or stand. He had no speech and interacted with parents occasionally. He was operated for undescended testes at 1 year of age. There was no history of hearing deficit and there were no seizures.

On examination at 5 years, the head circumference was 48 cm (-3.1 SD) and length was 99 cm (-2.3 SD), He had large anteriorly rotated ears, a broad nasal bridge, microphthalmia, thin upper lips and a pointed chin (Fig 2). He had a large mouth with downturned angles of mouth and prominent incisors. He had microphallus, scrotal hypoplasia and atrophic testes. He had axial hypotonia and the deep tendon reflexes were brisk. There was no organomegaly. His fingers were long and thin.

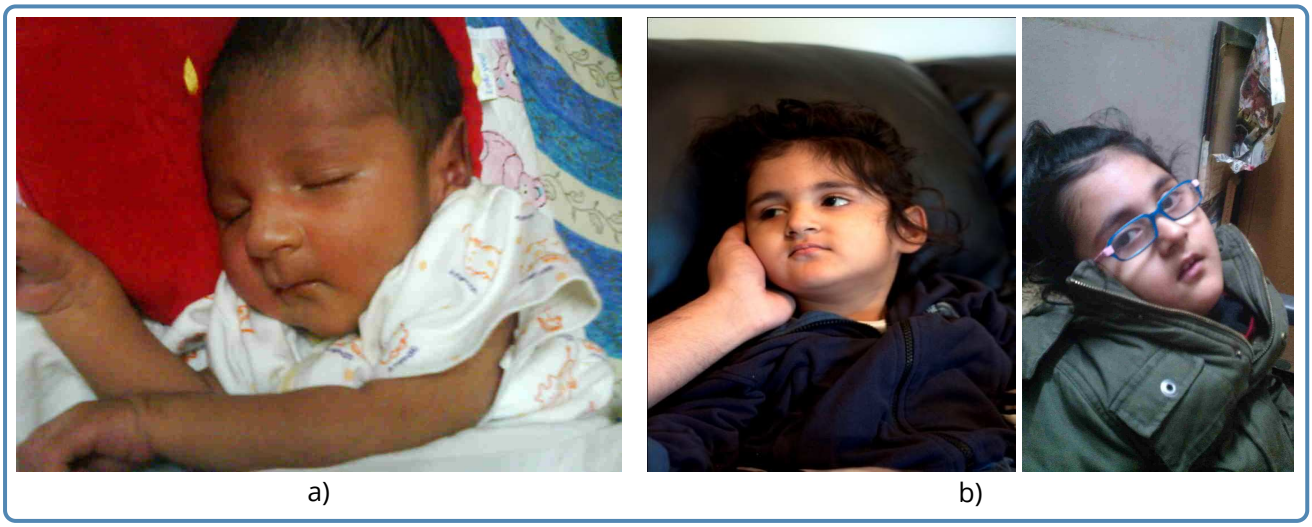
He was first evaluated at 6 months of age for developmental delay. His karyotype was normal (46, XY). In view of congenital cataract, he had been evaluated for galactosemia and plasma galactose and enzyme assay for galactose-1 phosphate uridyl transferase and epimerase were normal.

His MRI done at 20 months of age showed focal areas of signal alteration in subcortical and periventricular deep white matter of the bilateral frontal, parietal and peritrigonal occipital region and bilateral semiovale. There was associated partial agenesis of the corpus callosum.

In view of congenital cataract, hypoplastic genitalia and severe developmental delay, Micro syndrome was suspected and molecular genetic testing was done for confirmation. The patient showed homozygous loss of function mutation in exon 13 of the *RAB3GAP1* gene. This is a novel frameshift mutation c.1182.1183delCA (p.His394fs*9) not reported earlier and predicted to be pathogenic (Fig 3). It is not present in the ExAC database (`http://exac.broadinstitute.org/`). Both parents were heterozygous for this mutation consistent with their carrier status.

Case 3

This case is the sib of case 2. As mentioned above, the mother had come during pregnancy. Her USG



a) b)

Figure 2 a) and b): Face of Case 2 at age 1 week and at 5 yrs of age showing deep set eyes, broad nasal root, pointed chin and thin lips.

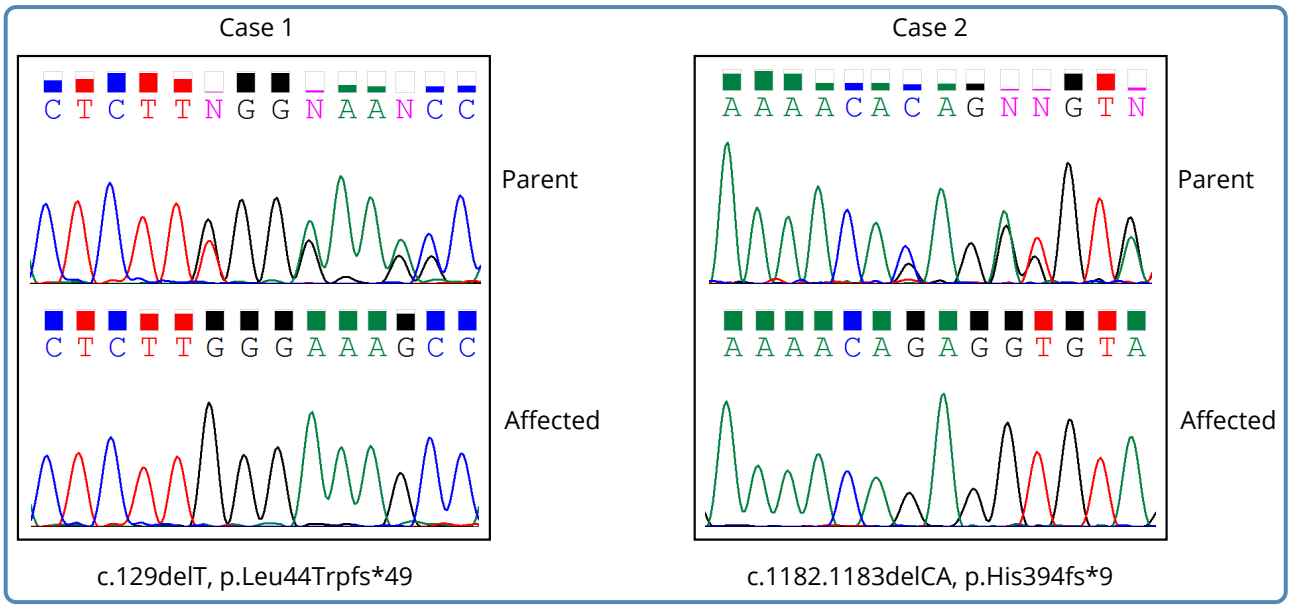


Figure 3 Chromatogram of *RAB3GAP1* mutation analysis of case 1 and 2 and their parents.

at 19 weeks gestation showed bilateral cataract in the fetus (Fig 4). There were no associated malformations. There was no fetal growth restriction. Biochemical screen for Down syndrome showed low risk for aneuploidy. Amniocentesis was done and PCR rubella and karyotype in the amniotic fluid sample were normal. The pregnancy was terminated in view of the history of cataract in the previous child (case 2). External examination of the fetus during autopsy evaluation showed cataract, pointed chin, thin lips and long philtrum (Fig 5). The fingers were long and thin. The fetus also had micropenis. After the disease-causing mutation in the *RAB3GAP1* gene was identified in the proband (case 2), mutation specific testing was done in the fetal DNA, which showed that the fetus was also

homozygous for the same mutation and thereby affected with Micro syndrome.

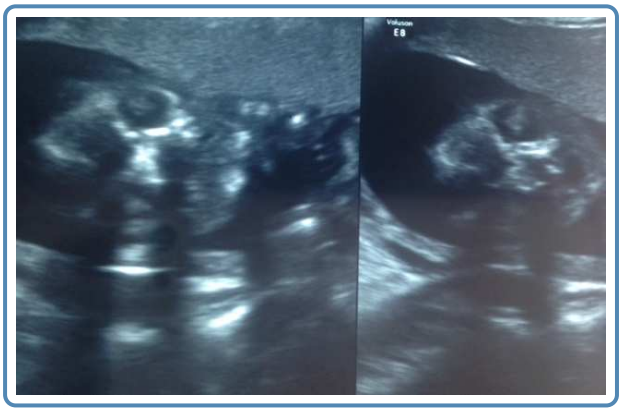


Figure 4 USG of case 3 at 19 weeks gestation showing cataract.

a) b)

Figure 5 a) and b): 19 weeks fetus with Micro syndrome showing cataract, broad nasal root and thin lips. Compare from Fig 2a (Case 2 at 1 week).

Discussion

Micro syndrome and Martsolf syndrome are autosomal recessive disorders with microcephaly and congenital cataract, first described in 1993 and 1978 respectively (Warburg et al., 1993; Martsolf et al., 1978). Warburg et al. were the first to report this syndrome in two siblings and a cousin from an inbred Pakistani family (Warburg et al., 1993). These children had microcephaly, hypogenitalism, cryptorchidism, borderline microphthalmia, microcornea, congenital cataracts, optic nerve atrophy, and retinal dystrophy. All had severe mental retardation and other findings, such as hypertrichosis, beaked nose with prominent nasal root, short philtrum, and prominent ears. The additional features in Martsolf syndrome are hypogonadism and cardiomyopathy. About 144 cases of Micro syndrome have been reported in the literature, and a broad consensus has emerged with regard to its presentation (Aligianis et al., 2005; Rodriguez Criado et al., 1999; Yuksel et al., 2007; Borck et al., 2011; Bem et al., 2011). Megarbane et al. (1999) reported 4 children from a highly inbred Muslim family from southern Lebanon with hypotonia, spastic diplegia, microcephaly, microphthalmia, congenital cataract, optic atrophy, ptosis, kyphoscoliosis, short stature, severe mental retardation, and cerebral malformations. Rodriguez Criado et al. (1999) discussed Micro syndrome in 2 sisters with microcephaly, microphthalmia, microcorneas, cataracts, sparse medial eyebrows, micrognathia, and severe psychomotor retardation. The parents were not related in this family.

In a study of 14 children with Micro syndrome, all from consanguineous families, Ainsworth et al. (2001) identified several consistent ophthalmic findings that they proposed might be pathognomonic for the syndrome: microphthalmia, microphakia, cataract, atonic pupils, mild optic atrophy, and severe cortical vision impairment. Bilateral lens opacity, unresponsive pupils, low-set and posteriorly angulated ears, broad nasal root, beaked nose, long philtrum, micrognathia, and high-arched palate were described by Derbent et al. (2004) in a 7 month old male Turkish patient. He also had bilateral cryptorchidism, micropenis, mental delay, truncal hypotonia, and increased muscle tone in both legs. Facial features were consistent with those originally described in the Micro syndrome. Yuksel et al. (2007) reported a 4-year-old Turkish boy with Warburg Micro syndrome. This child also had skin hyperextensibility, joint hypermobility, deformities of metatarsals in both feet, and overlapping toes. Combining information from the cases reported to date, the characteristics of Micro syndrome are mental retardation, microcephaly, congenital cataract, microcornea, microphthalmia, agenesis/hypoplasia of corpus callosum, and hypogenitalism (Dursun et al., 2012). Hypogonadotropic hypogonadism leads to cryptorchidism, micropenis, labioscrotal fusion,

Clinical feature	Literature	Case 1	Cases 2 & 3
IUGR	No	NA	No/No
Mental retardation	Yes	Yes	Yes/-
Postnatal microcephaly	Yes	Yes	Yes/-
Cataract	Yes	Yes	Yes/Yes
Prominent incisors	-	Yes	Yes/-
Thin upper lips	-	No	Yes/Yes
Limb spasticity	Yes	Yes	Yes/-
Broad nasal root	Yes	Yes	Yes/Yes
Prominent ears	Yes	Yes	Yes/Yes
Micropenis	Yes	No	Yes/Yes
Cryptorchidism/small testes	Yes	No	Yes/-
Hypoplastic corpus callosum	Yes	Yes	Yes/Yes
Polymicrogyria	Yes	No	Yes/-
Seizures	+/-	Yes	-/-

Table 1 Comparison of clinical features in our cases with cases described in literature.

and hypoplastic scrotum. Additional systemic manifestations included axial hypotonia with evolving limb spasticity, and occasional seizures.

All 3 cases in the present study had congenital cataract, and subtle facial dysmorphism. However, micropenis was not seen in case 1. Case 1 and case 2 had severe developmental delay. Table 1 shows clinical features of our cases as compared with the cases in literature. All cases of Micro syndrome reported in literature have hypoplastic genitalia, however, case 1 in this study had normal genitalia. Both case 1 and 2 had prominent incisors which has not been described earlier. Thin lips in cases 2 and 3 (sibs) and long slender fingers have not been reported earlier.

Micro syndrome can be diagnosed clinically on the basis of microcephaly, congenital cataract, and hypogenitalism (Dursun et al., 2012). Other conditions which should be excluded are CAMAK syndrome, CAMFAK syndrome, COFS syndrome, Cockayne syndrome, and Martsolf syndrome. CAMAK syndrome consists of cataract, arthrogryposis, microcephaly and kyphoscoliosis. CAMFAK is a syndrome of cataract, arthrogryposis, microcephaly, failure to thrive and kyphoscoliosis. COFS syndrome is characterized by brain atrophy with calcification, cataracts, microcornea, joint contractures, and growth failure. Cockayne syndrome is an inherited neurodegenerative disorder characterized by low birth weight, growth failure, brain dysmyelination with calcium deposits, cutaneous photosensitivity, cataract, and sensorineural hearing loss. Congenital cataract is also seen in Lowe syndrome and hence this should be excluded. Lowe syndrome is an X-linked recessive condition with congenital cataract and mental retardation along with renal dysfunction.

Various MRI findings have been described in patients with Micro syndrome. Pachygyria and corpus callosum abnormalities are present in majority of cases with Micro syndrome. Ainsworth et al. (2001) reported variable development of the corpus callosum, ranging from marked hypogenesis to normal in 1 patient along with some degree of pachygyria. Derbent et al. (2004) mentioned hypoplasia of the corpus callosum, diffuse cortical and subcortical atrophy, reduced myelinization, enlarged cisterna magna, and small orbits in brain MRI. Case 1 had agenesis of corpus callosum. MRI of case 2 showed focal areas of signal alteration in subcortical and periventricular deep white matter of bilateral frontal, parietal and peritrigonal occipital region and bilateral semiovale. There was associated partial agenesis of the corpus callosum. Pachygyria was also noted in the frontal and parietal regions.

Warburg Micro Syndrome is genetically heterogeneous and 4 types have been described.

Warburg Micro syndrome-1 is caused by mutations in the *RAB3GAP1* gene. Warburg Micro syndrome-2 is caused by mutations in the *RAB3GAP2* gene on chromosome 1q41. WARBM3 is caused by mutations in the *RAB18* gene on chromosome 10p12.1 whereas WARBM4 is caused by mutations in the *TBC1D20* gene on chromosome 20p13. Our patients had mutations in *RAB3GAP1* gene and hence they are Warburg Micro syndrome type 1.

RAB3GAP1 is implicated in regulating presynaptic neurotransmitter release in a Rab3-dependent manner (Muller et al., 2011). *RAB3GAP2* has been linked to the Rabconnectins, interacting partners that may function in the loading of synaptic vesicles with neurotransmitter (Nagana et al., 2002; Kawabe et al., 2003; Yan et al., 2009; Li et al., 2012). More recently the *RAB3GAP1-RAB3GAP2* complex has been shown to regulate *RAB18*.

Aligianis et al. (2005) reported inactivating mutations in the *RAB3GAP1* gene in 5 kindreds with Warburg Micro syndrome linked to chromosome 2q21.3, 2 of which had previously been described by Ainsworth et al. (2001). Investigation of an additional 10 families with Warburg Micro syndrome identified germline inactivating mutations in 7 families. Morris-Rosendahl et al. (2010) reported homozygosity for 5 different truncating *RAB3GAP1* mutations in 5 families from Turkish, Palestinian, Guatemalan and Danish background. Case 1 had homozygous mutation in exon 3 (Handley et al., 2013). Cases 2 and 3 (sibs) had novel homozygous mutation in exon 13.

Handley et al. (2013) provided an overview of the disease variants identified in the *RAB3GAP1*, *RAB3GAP2*, and *RAB18* genes, in 144 families with WARBM and 9 families with Martsolf syndrome. Mutations were identified in *RAB3GAP1* in 41% of cases, in *RAB3GAP2* in 7% of cases, and in *RAB18* in 5% of cases. Mutation details of case 1 mentioned here were included in this study. A recent study has reported the use of homozygosity mapping with single nucleotide polymorphism (SNP) microarray in identifying the causative gene and thereby in confirming the diagnosis of Warburg Micro syndrome in a consanguineous Indian family (Srivastava et al., 2015).

Antenatal diagnosis of bilateral cataract has not been reported earlier in Micro syndrome. The lens can be seen by the 12th week of pregnancy in both transverse and coronal scans of the skull. Normal lens is completely anechoic and can be identified by its strong anterior and posterior borders. When cataract is present, the boundary echoes are prominent and the substance of the lens becomes echogenic. The known syndromic causes of congenital cataract include Smith Lemli Opitz syndrome, Lowe syndrome, Alports syndrome and Conradi Hunnerman syndrome. Prenatal TORCH infection especially rubella accounts for about one third of cases of congenital cataract. Enzymatic disorders like G6PD deficiency, galactokinase deficiency, homocystinuria and galactosemia can also cause congenital cataract. In our case cataract was detected at 19 weeks of gestation (case 3). In another subsequent pregnancy of this couple, cataract was not seen and mutation analysis at 19-20 weeks gestation showed the fetus to be normal.

This series is presented to highlight the importance of evaluating a child with congenital cataract and developmental delay, for Micro syndrome, especially in families with consanguinity and positive family history and when the features are not typical of a congenital TORCH infection.

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