

# Micro syndrome

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## Abstract

*Micro syndrome is an autosomal recessive disorder characterised by ocular and neurodevelopmental defects and by microgenitalia. It presents with severe intellectual disability, microcephaly, congenital cataract, microcornea, microphthalmia, agenesis/hypoplasia of the corpus callosum, and hypogenitalism. Since its initial description, 26 cases of Micro syndrome have been reported in the literature. With exception of the ophthalmologic features, the clinical and dysmorphic findings are either unapparent or subtle in the early postnatal period. Mutations in RAB3GAP, a gene showing linkage to a region of homozygosity at 2q21.3, have been identified in some families. The RAB3GAP gene encodes a member of the Rab3 protein family, which is involved in regulated exocytosis of neurotransmitters and hormones. It has been suggested that the hypogenitalism is hypothalamic in origin, and that the ocular and neurodevelopmental defects result from abnormal neurotransmitter vesicular transport and exocytosis. Ocular findings are the most reliable diagnostic signs of Micro syndrome, especially during infancy. Pathognomonic ophthalmologic findings include microphthalmia, microcornea, cataract, atonic pupils, mild optic atrophy, and severe cortical vision impairment. Micro syndrome should be considered in any infant with congenital cataract. There is no specific treatment for Micro syndrome and the management is symptomatic. The conventional approach used for congenital cataract should be recommended.*

**Key words**

Micro syndrome, congenital cataract, microcornea, microphthalmia, corpus callosum, hypogenitalism, mental retardation, *RAB3GAP* gene.

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**Disease name and synonyms**

Micro syndrome, Warburg Micro syndrome, WARBM1

**Definition/diagnostic criteria**

Micro syndrome is an autosomal recessive disorder that is characterised by mental retardation, microcephaly, congenital cataract, microcornea, microphthalmia, agenesis/hypoplasia of the corpus callosum and hypogenitalism.

**Background**

Micro syndrome was first reported by Warburg *et al.* [1] in two siblings and a cousin from a consanguineous Pakistani family. The clinical and dysmorphic features of these patients were severe mental retardation, microcephaly, hypogenitalism, cryptorchidism, agenesis of the corpus callosum, hypertrichosis, beaked nose with a prominent nasal root, short philtrum, and prominent ears. One of the patients had lissencephaly. Ophthalmologic findings in the patients were borderline microphthalmia, microcornea, congenital cataract, optic nerve atrophy, retinal dystrophy and small pupils bounded by posterior synechiae [2-4].

**Epidemiology**

Since its initial description, 26 cases of Micro syndrome have been reported in the literature. The prevalence of the syndrome is unknown.

**Aetiology**

Micro syndrome is an autosomal recessive disorder. One recent study revealed that mutations in the *RAB3GAP* gene, which is linked to chromosome 2q21.3 and encodes RAB3 GTPase activating protein, are responsible for this syndrome [5]. The *RAB3GAP* gene is involved in regulated exocytosis of neurotransmitters and hormones. It has been suggested that the hypogenitalism is hypothalamic in origin and that ocular and neurodevelopmental defects are the result of abnormal neurotransmitter vesicular transport and exocytosis.

**Clinical description**

As mentioned above, the characteristic findings in Micro syndrome are mental retardation, microcephaly, congenital cataract, microcornea, microphthalmia, agenesis/hypoplasia of the corpus callosum and hypogenitalism. Although some patients display intrauterine growth retardation, most patients have a normal birth size and show postnatal growth retardation. Other than ophthalmologic features, clinical and dysmorphic findings are either unapparent or subtle in the early postnatal period.

Dysmorphic findings include prominent nasal root, short nose with upturned nares, short palpebral fissures, micrognathia, large ears or ears that are low set and posteriorly rotated, micrognathia, overhanging and long or small philtrum, and a highly arched palate. Simian line and hypertrichosis may also be seen.

Ocular findings are the most reliable diagnostic signs of Micro syndrome [6], especially during infancy. Suggested pathognomonic ophthalmologic findings for Micro syndrome include

microphthalmia, microcornea, cataract, atonic pupils, mild optic atrophy, and severe cortical vision impairment.

All patients display profound mental retardation, and hypotonia is always found during infancy. Agenesis/hypoplasia of the corpus callosum is one of the most prominent findings. Frontal polymicrogyria, pachygyria, lissencephaly, cortical and subcortical atrophy, ventriculomegaly, hypogenesis of the cerebellar vermis, large cisterna magna, myelinisation abnormalities, bilateral retinal colobomas, and peripheral neuropathy have been reported. Some patients with Micro syndrome may also have seizures. Tonic-clonic, myoclonic, and partial complex seizures, which may be intractable to anticonvulsant therapies, have been reported in these patients [7]. Patients may have limb contractures that become more prominent with age. Kyphosis or kyphoscoliosis may also be present [8].

Hypogenitalism and delayed puberty are major features of this syndrome. Micropenis, cryptorchidism, hypoplastic or absent labia minora, and clitoral hypoplasia may be seen. A few patients show kidney anomalies such as mild hydronephrosis, fusion of the lower poles, and ectopic left kidney.

### Natural history

Patients commonly have a normal birth size and show postnatal growth retardation. During infancy, mental-motor retardation and hypotonia are prominent. Limb spasticity usually develops within the first year of life. Later in life, joint contractures can be found in almost all patients. In the first decade of life, patients are unable to speak, or they are able to speak only a few words. They may be unable to walk and sit, and may not have sphincter control. Delayed puberty is seen, or pubertal signs may not be seen on follow-up. Optic atrophy becomes more obvious with increasing age [2-3,6,8].

### Diagnostic methods

A detailed ophthalmologic examination is necessary in any infant suspected of Micro syndrome. Ocular features are the most important clinical findings for the diagnosis. Brain magnetic resonance imaging (MRI) should be used to detect associated cerebral and cerebellar malformations. Renal ultrasonography should also be performed as a recent report on Micro syndrome described renal anomalies [4]. Molecular diagnosis is possible through analysis of the responsible gene, *RAB3GAP*, which is linked to chromosome 2q21.3 [5].

### Differential diagnosis

The differential diagnosis includes [Cockayne syndrome](#); [cerebro-oculo-facio-skeletal syndrome \(COFS\)](#) [8]; a syndrome involving [cataract, arthrogyrosis, microcephaly, and kyphoscoliosis \(CAMAK\)](#); a syndrome with [cataract, microcephaly, failure to thrive, and kyphoscoliosis \(CAMFAK\)](#); [Martolf syndrome](#) [9]; [Neu-Laxova syndrome](#); [Lenz microphthalmia syndrome](#) [10]; and [Smith-Lemli-Opitz syndrome](#) [11].

### Genetic counselling

Micro syndrome is an autosomal recessive disorder. A recurrence risk of 25% should be given to parents who have had an affected child.

### Antenatal diagnosis

No case of prenatally diagnosed Micro syndrome has been reported to date. There is no specific ultrasonographic finding that suggests Micro syndrome. Molecular diagnosis may become available after identification of the causative gene, *RAB3GAP* [5].

### Management including treatment

There is no specific treatment for Micro syndrome. The management is symptomatic. Some authors have recommended a conventional approach for the congenital cataract [6]. Ophthalmologic follow-up should be offered.

Physiotherapy is essential because all patients have hypotonia during infancy, and limb spasticity and contractures later in life [8]. Occupational and speech therapy is advised. Permanent assistance is required because of the lack of sphincter control and the wheelchair dependence of these patients. Antiepileptic therapy for seizures, and a consultation with a pediatric neurologist should be considered [2-3,6,8].

Data regarding the effectiveness of administering hormone replacement therapy at puberty are insufficient.

### Prognosis

Three patients with Micro syndrome died at 5, 11 and 15 years of age, but the cause of these deaths was not identified. Another patient died from respiratory failure at 8 years of age [2-4,6,8].

### Unresolved questions

The exact incidence of this syndrome is unknown. It is possible that some cases were misdiagnosed leading to underdiagnosis of this disease. The phenotypic spectrum may expand with further reports concerning Micro syndrome.

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