

# Microcephalia vera and microcephaly with simplified gyral pattern

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## Abstract

*Microcephaly is defined by an occipitofrontal circumference (OFC) below -2 standard deviation (SD) for age and sex. Severe microcephaly refers to an OFC < -3SD. Microcephalia vera (MV) and microcephaly with simplified gyral pattern (MSG) are genetic forms of isolated congenital microcephaly (< -3 SD at birth), with no extracerebral malformation. Their incidence has been estimated between 1/25 000 and 1/50 000 births.*

*In MV, the brain is abnormally small because of a reduced number of neurons, but is keeping (sub) normal gyral pattern and has no other gross pathological abnormality. Mental retardation is usually moderate and in most cases, patients have no systematized neurological defects or seizures. Brain weight typically is < 500 g (1/3 normal) and OFC is between 24 and 29 cm at birth (normal OFC being higher than 32 cm).*

*MSG has been misdiagnosed as MV or lissencephalies in the past. This disorder is defined by congenital severe microcephaly, reduced number and shallow appearance of gyri, and normal to thin cortex. Five types of MSG have been delineated on the basis of MRI and neurodevelopmental findings, but MV and MSG are likely to represent a continuous phenotype. Mental retardation ranges from mild and moderate (type 1) to severe (types 2 to 5). Pyramidal signs may be observed. Some forms (types 2 to 5) are associated with early-onset seizures and a poor prognosis.*

*MV and MSG are due to abnormal neuronal and glial proliferation. In both types, the cortex is of normal (2.5 mm to 4 mm) or reduced thickness and has normal cytoarchitectonic appearance, with 6 layers of neurons, which contrasts with microlissencephalies or lissencephalies with microcephalies, characterized by an abnormal cortical thickness and an anarchic cytoarchitectony.*

*MV and MSG are inherited in an autosomal recessive pattern. To date, no locus has been associated with MSG. Eight loci have been associated with MV and among those, three genes have been identified, MCPH1, ASPM, SLC25A19. There is no specific treatment for MV and MSG.*

**Key-words**

Microcephaly, lissencephaly, cortex, mental retardation, microcephalia vera, microlissencephaly with simplified gyral pattern.

**Disease name and synonyms**

- Microcephalia vera (MV);
- True micrencephaly;
- Radial microbrain;
- Microcephaly with simplified gyral pattern (MSG);
- Microlissencephaly (*partim*).

**Definition/Diagnosis criteria**

Microcephaly is defined by an occipitofrontal circumference (OFC) below -2 standard deviation (SD) for age and sex. Severe microcephaly refers to an OFC < -3SD.

MV and MSG are genetic forms of isolated congenital microcephaly (< -3 SD at birth), with no extracerebral malformation. In both types, the mantle is of normal (2.5 mm to 4 mm) or reduced thickness and has normal cytoarchitectonic appearance, with 6 layers of neurons. MV and MSG are likely to represent a continuous phenotype, mild MSG (at least) being seen in some patients from families with typical MV [Roberts *et al.*, 2002].

Clinically, their diagnosis is made by exclusion of other recognizable etiologies of microcephaly: toxic intrauterine exposure (maternal PKU, maternal alcohol consumption), infectious embryofetopathies (TORCHES), chromosomal anomalies.

**Excluded diseases**

- Microcephalies associated with multiple congenital anomalies syndromes and chromosomal disorders;
- Microlissencephalies (MLIS) (Norman-Roberts syndrome, Barth syndrome);
- Lissencephalies, classical and variants;
- Lissencephalies with cerebellar hypoplasia;
- Lissencephalies with agenesis of the corpus callosum (XLAG syndrome);
- Seckel syndrome and variants.

**Differential diagnosis**

MSG and MLIS share a similar smoothed brain shape, but differ by the ultrastructure of the cortical mantle: whereas in MV and MSG the mantle is of normal or reduced thickness and has normal cytoarchitectonic appearance, with 6 layers of neurons, in MLIS, the cortex is thickened (10 to 20mm) and has an anarchic cytoarchitectony, often with 4 neuronal layers only.

**Etiology**

A standard classification of malformations of abnormal cortical development [Barkovich *et al.*, 2001] divides lesions into those due to neuronal and glial proliferation in the germinal zones versus those due to cellular migration. As proliferation and migration occur synchronously, some of these abnormalities have overlapping features. Abnormal neuronal and glial proliferation lead to microcephalia vera (MV), microcephaly with simplified gyral pattern (MSG) [Barkovich *et al.*, 1998, Dobyns and Leventer, 2003] and, when combined with migration defect, these defects result in microlissencephalies (MLIS).

**Clinical description*****Clinical aspects of microcephalia vera***

MV describes genetic conditions in which the brain is abnormally small because of a reduced number of neurons, but is keeping (sub) normal gyral pattern and has no other gross pathological abnormality. Brain weight typically is < 500 g (1/3 normal - comparable with that of early hominids).

Very few data are available in the medical literature about MV. Moreover, MV and MSG have been mixed in the past, and, in many cases, there is no clinicopathological correlates. To our best knowledge, nothing has been published on cognition, behaviors or functional imaging in this group of patients. Mental retardation is usually moderate and in most cases, patients have no systematized neurological defects or seizures. Clinically, patients present with narrow, sloping forehead, and pointed vertex. Ears appear falsely large and protruding. By definition, there is no intrauterine growth retardation (IUGR), no postnatal growth retardation and no associated anomalies. Life span may be normal.

A unique, extremely rare form of severe microcephaly with early lethality and  $\alpha$ -ketoglutaric aciduria has been reported in the Amish community (Kelley *et al.*, 2002). To date, this disorder has not been reported in other populations.

***Clinical aspects of microcephaly with simplified gyral pattern (MSG)***

This disorder is defined by congenital severe microcephaly, reduced number and shallow appearance of gyri, and normal to thin cortex. Based on MRI and neurodevelopmental findings, 5 types have been delineated.

**Table 1** shows the Barkovich's classification of MSG:

cell cycle regulation in neural progenitors. It is mainly expressed in brain, liver and kidney. In

**Table 1: Barkovich's classification of MSG**

Type	Brain imaging	Clinical data
<b>Type 1</b>	Shallow sulci (? 50% of normal depth) Normal cortical thickness Normal white matter	Normal pregnancy and delivery Normal clinical aspect and neurological status (besides microcephaly) Mild, progressive corticospinal involvement (mild spasticity, Babinsky' reflex) Mild to moderate mental retardation
<b>Type 2</b>	Shallow cortical thickness (? 30% of normal thickness) Delayed white matter myelination	Normal pregnancy and delivery (excess of breech presentation?) At birth: feeding difficulties, hypo/hypertonia, abnormal reflexes Early-onset, generalized seizures Moderate to severe mental retardation Poor prognosis
<b>Type 3</b>	Very shallow sulci (<< 30% of normal depth) Normal cortical thickness Sub-epandyml neuronal heterotopias Normal white matter	Normal pregnancy and delivery At birth: feeding difficulties, hypo/hypertonia, abolished reflexes Neonatal seizures Severe mental retardation Poor prognosis
<b>Type 4</b>	Shallow sulci (? 50% of normal depth) Normal cortical thickness Normal white matter	Abnormal pregnancy due to abnormal intrauterine neurological status (hydramnios, arthrogyrposis,...) Normal pregnancy and delivery At birth: feeding difficulties, hypo/hypertonia, abolished reflexes, optocinetic nystagmus Neonatal seizures Severe mental retardation Poor prognosis
<b>Type 5</b>	Very small brain with enlarged subarachnoid spaces Less than 5, very shallow sulci (<< 30% of normal depth) Thinned cortex Sub-epandyml neuronal heterotopias Delayed white matter myelination	Normal pregnancy and delivery At birth: feeding difficulties, hypotonia, abolished reflexes Neonatal myoclonic seizures Severe mental retardation. Poor prognosis: usually lethal in weeks

### Genetics

MV and MSG are inherited in an autosomal recessive pattern. To date, no locus has been associated with MSG. Eight loci have been associated with MV and among those, three genes have been identified, *MCPH1*, *ASPM*, *SLC25A19*.

- ***MCPH1 - microcephalin (8p22-pter)***

The *MCPH1* gene has been cloned by homozygosity mapping in two consanguineous Pakistani families. It has been located to 8p23, consists of 14 exons and encodes a 835 amino-acid protein (microcephaline), which contains 3 BRCA1 C-terminal (BRCT) domains. Microcephalin could play a role in DNA repair or

mouse, it is expressed in fetal brain during neurogenesis (forebrain, germinative area). A unique S25X mutation in the first BRCT domain was reported, exclusively in inbred Pakistani families [Jackson *et al.*, 1998; Jackson *et al.*, 2002].

- ***MCPH5 – ASPM (1q31)***

The *MCPH5* locus mapping to 1q31 encodes the *ASPM* gene, a human ortholog of the *Drosophila melanogaster* "abnormal spindle" gene (*asp*), identified by homozygosity mapping and found responsible of roughly half of the MV cases in all ethnic backgrounds. It is a 62 kb gene with 28 exons, encoding a 3478 amino-acid protein, which contains multiples repeats of 20 amino-

acid sequence beginning with isoleucine (I) and glutamine (Q), called IQ repeat. The number of IQ domains seems related to the complexity of the central nervous system: roundworm: 2 IQ; drosophila: 24 IQ; mouse: 61; human: 72-80. All published mutations lead to loss of function [Pattison *et al.*, 2000; Jamieson *et al.*, 2000; Bond *et al.*, 2002].

- **SLC25A19 (17q25)**

The *SLC25A19* gene is responsible of the Amish type of MV, a unique autosomal recessive disorder observed in Amish presenting with extreme microcephaly (-6 to -12 SD) and associated with  $\alpha$ -ketoglutaric aciduria. *SCL25A19* codes for a deoxynucleotide carrier (DNC) [Rosenberg *et al.*, 2002].

- **Other loci**

Several other loci have been mapped for MV. These include MCPH2 (19q13.1-13.2) - [Roberts *et al.*, 1999], MCPH3 (9q34) [Moynihan *et al.*, 2000], MCPH4 (15q) [Jamieson *et al.*, 1999], MCPH6 (13q12.2 – Ferraz-Real, in press), and MRXS9 (Xq12-q21.31) [Shrimpton *et al.*, 1999]. About 20% of families are still not linked to any loci.

### Diagnostic methods

Diagnosis relies on MRI scan. *ASPM* mutation screen may be available in some laboratories.

### Frequency

Incidence of congenital microcephaly < -2 SD is about 3/100 to 4/100. Congenital microcephaly  $\leq$  -3 SD occurs in about 1-2/1 000 births. There is no recent reliable estimate of developmental microcephalies incidence among those, although a rate of 1/25 000 to 1/50 000 births is proposed in the old literature.

### Genetic counseling

Due to the autosomal recessive inheritance pattern of MV and MSG, recurrence risk is 1/4.

### Antenatal diagnosis

Prenatal diagnosis can be performed through fetal imaging. Slow head circumference growth in a child with otherwise normal intrauterine growth evokes the diagnosis (after exclusion of TORCHES, chromosomal defect and maternal PKU and toxic exposure). Fetal profile on ultrasound scan may confirm sloping forehead. Fetal brain MRI can be used to confirm MSG. Delayed formation of sulci can only be detected after 26 weeks, and confirmation often requires imaging after 30 weeks of gestation.

In families where a mutation in one of the causative genes is identified, chorionic villus sampling (CVS) can be performed for DNA

analysis. Currently, due to genetic complexity, DNA diagnosis is not technically feasible for sporadic cases detected during intrauterine growth.

### Management including treatment

There is no specific treatment for MV and MSG. For MV and MSG type 1, special schooling is required. Speech therapy physiotherapy and early psychomotor support should be provided to patients according to developmental level.

For patients with MSG type 2 to 5, anticonvulsive therapy is often mandatory, and seizures may be difficult to relieve. Nasogastric tube feeding and other basic supportive care may be required for babies with the most severe neurologic impairment.

### Unresolved questions

Genetic heterogeneity of MV and MSG is still a field of research.

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