

PRIMORDIAL OSTEODYSPLASTIC MICROCEPHALIC DWARFISM TYPES I, II AND III

DESCRIPTION :

Microcephalic osteodysplastic dwarfism (MOPD) of types I, II and III belongs to the family of "primordial dwarfism". MOPD types I and III were previously thought of as two distinct forms. However, recent studies show that they are the same syndrome. Therefore, we will only refer to type I to refer to types I and III.

The affected genes differ according to the form of the condition: Type I is caused by mutations in the RNU4ATAC gene, and type II is caused by mutations in the PCNT gene.

People with type I usually die within the first few years of life. Those with type II present a very severe form of dwarfism: in adulthood, they are usually less than one meter (3'3") tall.

The diagnosis is extremely rare and is an autosomal recessive trait [see "Genetics"]. Prevalence is unknown in Type II with more than 150 cases worldwide. Less than 60 cases of Type I have been described as of 2020.

CHARACTERISTICS AND DIAGNOSIS :

Osteodysplastic microcephalic dwarfism is characterized by intrauterine growth inhibition (starting before birth). Affected individuals have severe proportionate dwarfism whose characteristics include:

- Microcephaly (small head);
- Spondylo-epimephyseal dysplasia (abnormal skeletal growth);
- Facial dysmorphism: small jaw (micrognathia), receding forehead, bulging eyes and prominent nose with flat nasal bridge (type I)/ protruding nose and small pointed chin (type II);
- Short limbs;
- Sparse hair and eyebrows (type I);
- Dry skin (type I);
- Intellectual deficit (type I, with type II the deficit is absent or slight);
- Abnormally small teeth (type II).

It should be noted that there is clinical overlap with other conditions, also caused by a mutation in the RNU4ATAC gene, namely Roifman syndrome (with antibody deficiency) and Lowry-Wood syndrome (less severe form).

In the case of MOPD I and II, short stature is visible from birth or even before. A radiological examination allows the diagnosis to be made. In type II, small bones are observed with metaphyses (growth plates located under the head of the bone) that enlarge abruptly. The



femoral heads are small and dislocated with a coxa vara (irregularity of the femur). There may also be dislocation or subluxation of the knees. The iliac wings (large pelvic bones) are narrow. The bones of the forearm are short and curved; the ulna is shortened and its metaphyseal limit is very wide, like that of the radius. In adulthood, the bones are slender and the epiphyses (heads of bones) are small. The ribs widen in a palatal pattern and the vertebrae have slightly concave plateaus.

In Type I, there is dislocation of the hips and elbows. The limbs are short and show an abrupt widening of their metaphyseal limits (growth plates located under the head of the bones). The iliac wings (large pelvic bones) are square. The development of the spine is delayed and is characterized by an enlargement of the intervertebral spaces. There are also significant bone irregularities (no epiphysis is visible).

Finally, several cerebral abnormalities are noted (lissencephaly, hypoplasia of the frontal lobes and agenesis of the corpus callosum or cerebellar vermis).

MAIN POSSIBLE COMPLICATIONS :

a. Type I:

Infants with Type I can have seizures and apnea episodes. If they do not die in the perinatal period, these children usually die in the very first years of life from infection or respiratory failure.

b. Type II:

Café au lait spots: These may occur in infants with osteodysplastic microcephalic dwarfism type II. These stains take the form of regular, oval-shaped, light to dark brown marks. The café au lait spots are benign. They may become darker during childhood or with exposure to sunlight, but this is not a cause for concern.

Eyes: Farsightedness may occur. Common symptoms include difficulty concentrating; blurred vision during prolonged periods of reading and writing; eye fatigue; headaches after a task that requires staring for a long period of time, such as working at a computer; discomfort or pain in the eyes when performing near tasks that require a greater effort to accommodate. Farsightedness is best corrected with glasses or contact lenses.

Scoliosis: In some cases, children with osteodysplastic microcephalic dwarfism type II can develop scoliosis (a three-dimensional irregularity of the spine). Clinical monitoring should be performed regularly. It must be accompanied by X-rays as soon as any doubt arises.

Diabetes: Resistance to insulin and then diabetes often develops during growth, usually around the age of 4 years. Insulin resistance is initially asymptomatic, as the pancreas may initially compensate. Diabetes can then develop insidiously. Once it has taken hold, the



symptoms of diabetes appear: fatigue and/or drowsiness, an increase in the volume and frequency of urine, intense thirst and exaggerated hunger, unexplained weight loss, blurred vision, slow healing, genital and bladder infections, tingling in the fingers or feet, and irritability. These signs reflect blood sugar levels above normal. Diabetes is a serious problem that must be managed to avoid complications, including damage to the eyes, kidneys, nerves or heart.

Increased risk of cerebrovascular disease: Depending on the source, between 20% and 50% of children with osteodysplastic microcephalic dwarfism type II may be affected by Moyamoya syndrome, a chronic cerebrovascular diagnosis characterized by stenosis (narrowing) and progressive occlusion of the cerebral vascular system at the base of the brain. As a result, people with this condition are at risk for one or more strokes. The main symptoms of Moyamoya include headaches, dizziness, seizures, vision or language problems, and paralysis of a limb (arm or leg). Stroke is a life-threatening emergency. Signs of stroke include facial slumping, slurred speech, a sudden and severe headache, numbness or paralysis (often on one side of the body).

Because of these risks, people with osteodysplastic microcephalic dwarfism type II should be screened for cerebrovascular disease every 12 to 18 months. If a problem is discovered, revascularization surgery may be considered.

TREATMENT:

The management of osteodysplastic microcephalic dwarfism is multidisciplinary (surgery, occupational therapy, orthopedics, child psychiatry, physiotherapy, etc.) and preventive, and is essentially aimed at detecting complications and enabling those affected to have a better quality of life.

Currently, there is no specific treatment for this form of dwarfism. Limb lengthening, a controversial practice, is not recommended. In addition to the complications and pain limb lengthening can create, this technique can also create a body imbalance in people with osteodysplastic microcephalic dwarfism.

List of the main elements to be monitored and managed (type II of the diagnosis):

- Spondylo-epimephyseal dysplasia;
- Intellectual impairment (if present) and microcephaly;
- Hyperopia;
- Scoliosis;
- Diabetes;
- Risk of cerebrovascular disease.



RESOURCES :

Association québécoise des personnes de petite taille

<https://www.aqppt.org/>

Little People of Ontario

<https://littlepeopleofontario.com/>

Regroupement québécois des maladies orphelines - Centre iRARE

<https://rqmo.org/centre-dinformation-et-de-ressources-en-maladies-rares/>

Orphanet :

Fact sheet on osteodysplastic microcephalic osteodysplastic dwarfism type I and III

https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=en&Expert=2636

Fact sheet on osteodysplastic microcephalic dwarfism type II

https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=en&Expert=2637

GARD – Genetic and Rare Disease Information Center

<https://rarediseases.info.nih.gov/diseases/5120/microcephalic-osteodysplastic-primordial-dwarfism-type-1>

OMIM - Online Mendelian Inheritance in Man:

Fact sheet on osteodysplastic microcephalic osteodysplastic dwarfism type I

<https://www.omim.org/entry/210710>

Fact sheet on osteodysplastic microcephalic osteodysplastic dwarfism type II

<https://www.omim.org/entry/210720>



Please contact us for more information

Association québécoise des personnes de petite taille
6300, avenue du Parc, bureau 430, Montréal (Québec) H2V 4H8

Phone: 514 521-9671 • Fax: 514 521-3369

Website: www.aqppt.org • E-mail: info@aqppt.org

Avec la participation financière de

Office des personnes
handicapées
Québec The logo for the Office des personnes handicapées Québec features the word 'Québec' in a large, serif font, followed by four small icons arranged in a 2x2 grid. Each icon is a stylized fleur-de-lis.