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Miller Syndrome: About A Case

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Abstract: Oto-mandibular dysplasias are malformations involving hypoplasia or agenesis of the ear and mandibular hypoplasia. On the genetic level, it is a group of very diverse, sometimes hereditary, affections with different possible or sometimes isolated modes of transmission within a family. We report a case of Miller syndrome (Genée-Wiedemann syndrome) in a 12-year-old girl associated with perceptual deafness. The patient presented facial dysmorphism with bird head facies. There is also a hyperthelorism with effacement of the nasogeneic fold and an important micrognatie and mandibular retrognatia. At the otological examination, microtiters are present with low implanted and poorly hemmed ears without pretragian tubercles or preauricular fistulas. The acoustic external meatus is stenosed, which does not allow the eardrums to be visualized. The auditory balance shows a right endocochlear involvement with abolished PEA on the left. On the CT of temporal bone we notice a bilateral malformed aspect of the acicular chains with hypoplasia of the long processes of anvils and stirrups more marked in the left side. The genetic opinion is in favor of an oto-mandibular syndrome: Miller given the presence of malformations of the upper right extremity. Associated extrafacial malformations that are often present but unrecognized as well as the nature of the facial involvement and the symmetrical or asymmetrical character will allow to recognize certain specific genetic syndromes. Only the constitution of a family tree, a detailed clinical examination and sometimes some complementary examinations make it possible to identify these syndromic forms. The presence of abnormalities of the extremities associated with the facial involvement makes it possible to distinguish acrofacialdysostoses (Miller and Nager syndrome) which are genetically distinct from other oto mandibular dysplasias.
Keywords: Acrofacialdysostoses; Miller syndrome; Genie-Wiedemann syndrome.

INTRODUCTION

Oto-mandibular dysplasias are malformations involving hypoplasia or agenesis of the ear and mandibular hypoplasia. On the genetic level, it is a group of very diverse, sometimes hereditary, affections with different possible or sometimes isolated modes of transmission within a family.

OBJECTIVE, PATIENT AND METHODS

We report a case of Miller syndrome (Genée-Wiedemann syndrome) in a 12-year-old girl associated with perceptual deafness. The child is born of a not followed pregnancy without notion of medication taken by the mother. There is also a notion of second degree consanguinity.

The history of the disease dates back to birth by a difficulty in breastfeeding with suction, swallowing, ventilation disorders and fake roads and ebb feeding through the nasal cavities. In addition, the mother reports a notion of nocturnal ronchopathy with rhinolalia and a more marked hypoacusia on the left, all of which evolve in a context of stunting with slight mental deficit.

The clinical examination shows facial dysmorphia with bird-head facies (Figure 1). There is also a hyperthelorism with obliteration of the nasolabial fold and significant micrognathia and mandibular retrognation. In the oral examination, there is a limitation of the mouth opening at 2 cm, posterior velar cleft, dental relation class 2, dental overlap and glossoptosis.

Fig-1: facial dysmorphism with bird head face

At the otological examination, microtitis is present with low implanted and poorly hemmed ears without pretragian tubercles or preauricular fistulas. The acoustic external meatus is stenosed, which does not allow the eardrums to be visualized. At the acoumetry: Deafness of perception more marked on the left: negative Rinne on both sides and Weber lateralised on the right.

There is no abnormality on ophthalmological examination. On osteoarticular examination there is a shortening of the right upper limb and a bilateral Oligodactyly of the 5t finger (Figure 2). The neurological examination is normal.

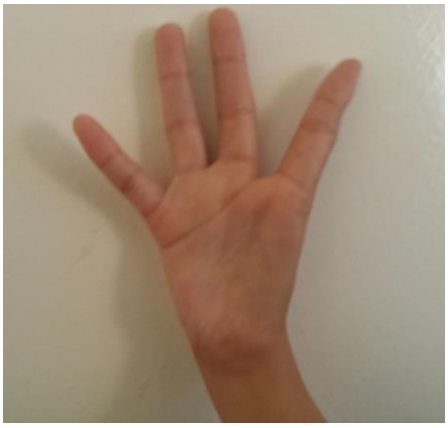

Fig-2: Oligodactyly: absence of the fifth digit

On the orthopantomogram we note the presence of supernumerary teeth. We note on the face CT an important retrognathism. Bilateral hypoplasia of both ramus and mandibular condyles (Figure 3) with slightly hypertrophic appearance of the coronoid processes and Right maxillary sinus hypoplasia associated with Hypoplasia of right and left zygomatic arches.

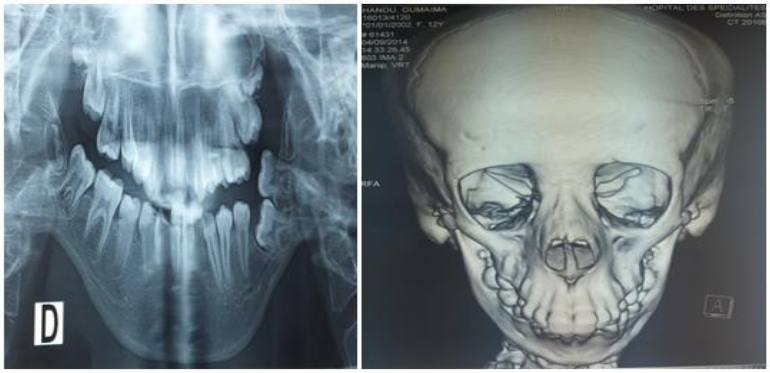

Fig-3: Important retrognathism. Bilateral hypoplasia of both ramus and mandibular condyles

The auditory balance shows a right endocochlear involvement with abolished PEA on the left. On the CT of petreous bone (figure 4) we notice a bilateral malformed aspect of the ossicular chains with hypoplasia of the long processes of anvils and stirrups more marked in the left side.

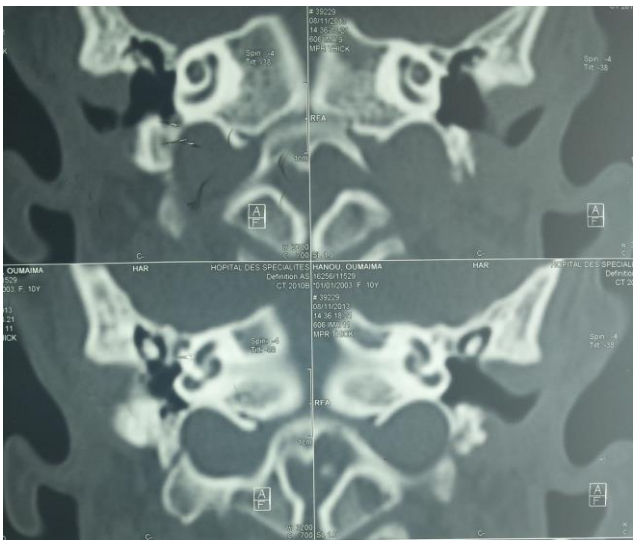

Fig-4: Malformed aspect of the ossicular chains with hypoplasia of the long apophyses of the anvils and stirrups

On echocardiography we notice a minimal tricuspideal insufficiency and on Abdominal Ultrasound: Ectopic kidneys, low located, with aspect evoking horseshoe kidneys. These ectopic kidneys are diminished in size poorly differentiated.

The genetic opinion is in favor of an oto-mandibular syndrome: Miller given the presence of malformations of the upper right extremity.

DISCUSSION

The nature of the facial lesion and the extrafacial malformations will make it possible to recognize certain specific genetic syndromes. Only the constitution of a family tree, a detailed clinical examination and sometimes some complementary examinations make it possible to identify these syndromic forms. The presence of extremity abnormalities associated with facial involvement distinguishes acrofacial dysostoses (Miller and Nager syndrome) which are genetically distinct from other oto-mandibular dysplasias [1].

The facial abnormalities of the miller syndrome include an anti-fungal orientation of the palpebral fissures, malar and mandibular hypoplasia, and abnormalities of the outer ear very close to Franceschetti syndrome [2], but with involvement of the upper part of the face (zygomatic arch) much less important and usually an absence of palpebral coloboma but may be limited to mandibular hypoplasia with discrete orientation at the bottom and outside of the palpebral fissures.

The anomalies of the extremities are of the post-axial type: absence of the 5th rays in the hands and feet, syndactyly [3]. Intellectual development is normal, but conductive deafness may exist. Genetically, miller syndrome appears to be sporadic, but familial cases with dominant transmission have been reported [4]. Recidivism in siblings born to unaffected parents has suggested recessive inheritance in some cases, suggesting heterogeneity in this group.

Miller syndrome was the first Mendelian disorder whose molecular basis was identified via whole-exome sequencing and shown to correlate with mutations in dihydroorotate dehydrogenase (DHODH) [5]. Recently additional biallelic mutations in DHODH were identified in a further four unrelated families with typical clinical features of Miller syndrome [6]. To date, a total of 14 distinct mutations in the coding region of DHODH, including 2 nonsense mutations, have now been identified [6]. DHODH is a monofunctional protein which, in most eukaryotic organisms, is located on the outer surface of the inner mitochondrial membrane, and catalyzes the fourth enzymatic step in de novo pyrimidine biosynthesis. The human DHODH gene, which is reported as the causable gene of Miller syndrome, was cloned in 1992. This gene exists in various species [7].

The malformations observed in individuals with Miller syndrome could be caused by perturbed NF-kB signaling due to loss of the DHODH function. TCOF1 and DHODH genes are quite different; however, mutations in either gene can cause similar dysfunctions of cell proliferation, migration, and differentiation. So, these mutations would lead to similar phenotypes. Miller syndrome had been hypothesized to be an autosomal recessive disorder [5].

The treatment of Miller syndrome depends on the specific symptoms in each individual and requires

the coordinated efforts of a multidisciplinary healthcare professional's team: Pediatricians, plastic surgeons, pediatric otolaryngologists, ophthalmologists and psychologists o treat and ameliorate a lifetime of specific problems.

CONCLUSION

Only a detailed and complete clinical examination of the subject with oto-mandibular dysplasia often associated with complementary examinations (spine radio, echocardiography, etc.) and specialized advice (ENT consultation, maxillofacial, ophthalmology, genetics etc.) can identify a syndromic form and detect associated malformations within specific management.

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