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# Melnick Needles Syndrome: Computed Imaging and Management Difficulties

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## Abstract

Melnick-Needles syndrome is an osteo-dysplasia caused by a mutation of a gene, FLNA, coding for filamine A. It is at the origin of a set of complex congenital malformations, mainly of interest to the members, but also to the cranio-facial region. Melnick-Needles syndrome was first described in 1966 by two Americans John Melnick, a radiologist, and Carl F Needles, a pediatrician. They described cases of families of several generations who had a characteristic severe congenital bone disorder. They thought that human-to-human transmission had occurred in one case. We report a case of Melnick-Needles syndrome which is a pathology with very high mortality especially in a male subject. This was an observational study of a case received in consultation with the pediatric service of the Souro Sanou University Hospital Center in Bobo Dioulasso in Burkina Faso. It was a 3-year-old boy born in a low-term pregnancy without any prenatal consultation, imaging test and prenatal biology performed. The exact pathogenesis of this condition is not established but is linked to a mutation of the Filamine A gene linked to sexual chromosomes X. Pathology is rare, around a hundred cases have been reported worldwide. Its incidence, according to the literature is around 1/100,000. The sex ratio is at 7. The malformations of this acquired embryo-fetopathy are multiple, polymorphic and asymmetrical. The diagnosis of this pathology is suspected by the clinic and established by molecular biology by sequencing the genes responsible for the mutation. However, imagery, in particular the scanner has a major role by its protocol with multi-planar reconstructions and its analysis in double windowing which allow a better description of the malformations of this syndrome. Its management is complex, and multidisciplinary, and the unfortunate prognosis in our context is because of the precarious technical platform. In our case despite the obvious

malformations presented by the patient, the parents consulted late in a health center because of the automation and especially the socio-cultural constraints which incriminate this type of polymalformation as being a curse. The patient underwent abdominal surgery and even the operating procedures were simple, he died four months after leaving the hospital, due to an unspecified cause.

## Keywords

Melnick-Needles Syndrome, Polymaformation, TDM, Burkina Faso

## 1. Introduction

Melnick-Needles syndrome is part of a group of related conditions called opta-latodigital spectrum disorders, which also includes type 1 and type 2 otopalato-digital syndrome, fronto-metaphysal dysplasia and terminal bone dysplasia [1] [2]. It is an extremely rare osteo-dysplasia with a prevalence of less than 1/100,000 [1] [3].

Coste *et al.* in 1968 proposed the term "Osteodysplasty" in a 58-year-old woman affected with a striking face including frog-shaped eyes, full red cheeks, a prominent forehead, and a fleeing chin. Melnick-Needles syndrome is the cause of complex congenital malformations, mainly of interest to members, the cra-nio-facial region and the thoraco-abdominal axis [4] [5]. It seems to affect more women than men with a sex ratio of 7. [6]. It was first described in 1966 by two Americans, John Melnick, a radiologist, and Carl F Needles, a pediatrician [7]. The x-ray noted long curved bones, tortuous ribbon ribs, collarbones, shoulder blades and a deformed pelvis [4] [8].

Beighton and Hamersma in 1980 hypothesized that fronto-metaphyseal dys-plasia and osteo-dysplasia may be due to the same gene [9]. They suggested that the gene could be linked to chromosome X. They noted that the protests in the two families of Melnick and Needles were variable and that no transmission from man to man was reported. It is due to a disorder in the X chromosome and causing skeletal development abnormalities and other health problems such as intracranial and intra-abdomino-pelvic abnormalities [1]. The exact pathophysi-ology of the disease remains unknown. Clinical diagnosis is not always easy, it is confirmed by biology. However, this diagnosis can be evoked with the imagery at the start of an adequate lesion description. The objective of our work was to describe the imaging aspects of a case of Melnick-Needles syndrome diagnosed at the Souro Sanou University Hospital Center (CHU-SS).

## 2. Observation

It was a 03-year-old boy, the first child of a couple who was referred to the pe-diatric ward for recurrent dyspnea on polymalformative syndrome. Obstetric history noted an absence of prenatal consultation, biological examinations and medical imaging during pregnancy. Childbirth was carried out at home by a vil-

lage birth attendant. There was no post-natal consultation in health training despite the presence of an obvious abdominal malformation. The newborn had recurrent dyspnea with a delay in physical development.

The persistence and worsening of respiratory disorders had motivated parents to consult in a health and social promotion center, from where the child was referred to the CHU-SS. At the clinical examination, we noted:

- A general condition preserved with apyrexia and normal blood pressure figures
- A facies describing minimal exophthalmia and full cheeks
- A prominent front
- A thoracic cyphosis
- A genu varum with arched lower limbs
- A depressible left para-ombilical subcutaneous mass, reluctant and painless
- Staturo-ponderal growth retardation.
- He was 70 cm tall for a weight of 7.4 kg and had a hearing impairment.
- The biological balance sheet carried out was without anomaly.
- An entire body or body scan was performed in our patient for a better lesion description; we carried out a three-phase helical acquisition without and with injection of iodized contrast product at the rate of 2 ml/kg of body weight. Scanographic exploration was carried out using a SIEMENS brand aircraft of 62 barrettes. The imaging analysis was performed in a parenchymal and bony window. The scanner made it possible to describe:
- A communicating type hydrocephalus;
- A prominent front;
- A left anterolateral omphalocele;
- A diaphragmatic hernia with the presence of a portion of the left liver in the chest;
- Homogeneous hepato-splenomegaly;
- A fine and wavy appearance in the shape of "ribbon" of the last ribs;
- A thoracic cyphosis;
- A diastasis of the pubic symphysis by hypoplasia of the pubis and the ischion;
- An arched aspect of pelvic limbs.

These different pathological aspects are imagined in **Figures 1-3** which describe the radiological semiological characteristics.

Faced with clinical and radiological arguments, the diagnosis of the spectrum disorder of oto-palato digital syndrome was mentioned in its clinical form of Melnick-Needles syndrome. To confirm this hypothesis we have carried out genetic analyzes. The sequencing of the target exon revealed a heterozygous mutation of the FLNA gene, c 3476 T > C, p. Lys 1086Pro which confirmed the diagnosis. The patient was referred to pediatric surgery for treatment. He underwent abdominal surgery. The operating procedures were simple and the patient was released from the hospital after three weeks of hospitalization. He is said to have died a few months after their return home due to an unspecified cause.

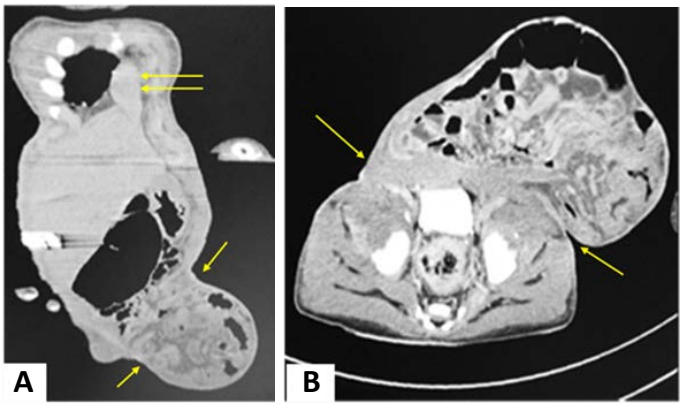


**Figure 1.** Body scan, portal phase, parenchymal window, axial section (B), coronal reconstruction (A). Left anterolateral omphalocele (A, B, arrows), and diaphragmatic hernia of part of the liver (A, double arrow).

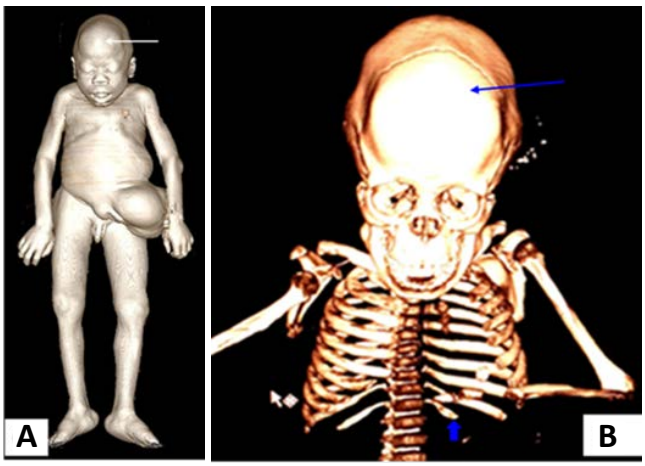


**Figure 2.** Body scan, VRD reconstruction and 3D bone window; a prominent forehead (A, B arrow), a "ribboned" appearance of the last ribs (B arrowhead).

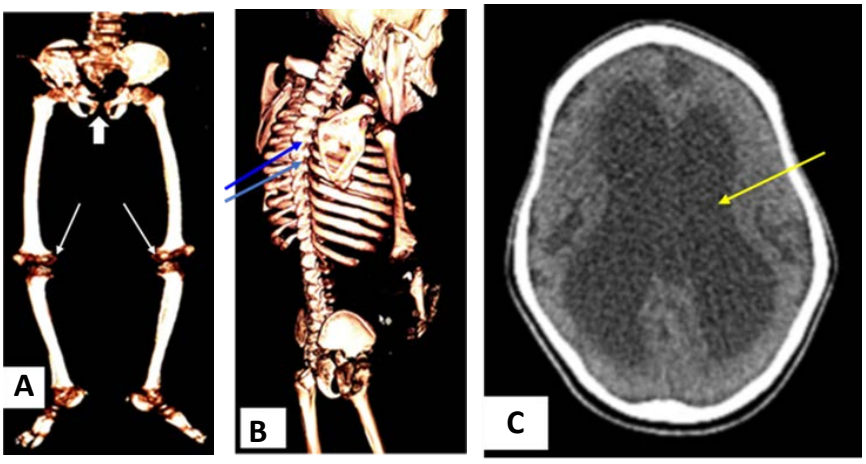


**Figure 3.** 3D body scan, bone window (A, B), parenchymal window, cerebral axial section (B); thoracic kyphosis (A, double arrow), symphysis pubis diastasis (B, arrowhead), "arched" appearance of thepelvic limbs (B, arrows), dilatation of the lateral ventricles (C, arrow).

## 3. Comments

Epidemically, NMS is described as a rare pathology, since its prevalence is estimated to be less than 1/100,000 births [1] [3]. In Burkina Faso, no study related to this pathology has yet been carried out. However, this syndrome also seems rare there because we have not found any request for a test for gene mutation of the FLNA in the molecular biology services of the university hospitals of our country.

Since NMS is a congenital pathology, its diagnosis is made during early childhood, but nevertheless due to its very minor phenotypic expression in certain female subjects it can be diagnosed at any age according to the literature. Our patient was 3 years old when the diagnosis of NMS was made which confirms the data in the literature [2].

Between the two sexes there is a female predominance with a sex ratio equal to 7 [6]. However, our patient was male and other authors such as Van der Lely *et al.*, Nevin NC *et al.* also described cases of NMS in a male subject [7] [10].

The phenotypic spectrum of NMS is linked to mutations in the FLNA gene which codes for a cytoskeleton protein, according to the recessive mode linked to X with a lesser expression in women [1] [11] [12] [13]. The FLNA comprises 48 exons and encodes a modular protein with an N-terminal actin-binding domain and a tail of 24 structurally homologous repeats [8]. Filamin-mediated cellular functions include linking signal transduction events to actin cytoskeleton modulation and gene transcription [14]. We noted in our patient a mutation at the level of the fortieth exon of the FLNA in accordance with the data of the literature and which was at the origin of the Melnick-Needles syndrome. In 2003, Robertson *et al.* reported that MNS is due to gain-of-function mutations in the FLNA gene and an X-linked mode of inheritance. They also noted that the mutations are responsible for the otopalatodigital syndrome of type 1, otopalatodigital syndrome type 2, fronto-metaphyseal dysplasia and terminal bone dysplasia with or without skin pigmentation defect [10] [11] [14] [15].

In the literature review, no typical radiological description of our illustration was notified. However, we have had documented cases of Melnick-Needles syndrome where associated malformative abnormalities such as omphalocele have been notified in a female subject without notified diaphragmatic hernia [6]. In most of the documented cases of NMS in the male subject, it appears that the newborn dies in the immediate postpartum, which was not the case for our patient who survived to the age. 03 years without any appropriate medical follow-up. Medical imaging plays a very decisive role in its diagnosis with a precise description of the various malformations associated with it. It thus allows a better management and an evolutionary follow-up of this affection. The phenotypic variability in Melnick-Needles disease requires associated imaging means including standard radiography, computed tomography, antenatal and postnatal ultrasound and especially MRI because of its better tissue contrast, particularly in optimal exploration. neurological and vascular. For our patient, the contribu-

tion of standard radiography was limited, particularly in the analysis of the left latero-umbilical mass. The CT scan was performed and made it possible to make a complete assessment of all the malformations. In our case, the socio-cultural constraints did not allow the mother to have a good follow-up of her pregnancy, which led to a delivery outside a health center. Despite these obvious malformative anomalies visible at the abdominal level in the newborn, there was no immediate consultation in a health center. The first consultation in a health center occurred in the 3rd year after childbirth with the onset of recrudescent respiratory disorders. From there, he was referred to the Sourou Sanou university hospital center for better management of the clinical malformation abnormalities on examination. The clinical malformation syndrome of our patient required in first intention the prescription of a body scan for an exhaustive description of all malformation anomalies that could be associated. This body scan facilitated the evolutionary follow-up of this malformative condition during the surgical treatment.

The pathogenesis of NMS has not been established. Some researchers have reported an increase in skeletal collagen content which may explain the sclerosing bone process while others have suggested that it is related to a generalized connective tissue disorder due to hyperlaxity of the skin and joints [16] [17]. The literature notes that the association of omphalocele during NMS is very common in male subjects and this has been confirmed in our case [1] [6]. Urological and cardiac involvement are also common in patients with NMS, which was not the case in our patient [18] [19]. This is explained by the phenotypic diversity described in patients with this syndrome according to the literature [20]. It is not yet known why phenotypes may differ between women with NMS. Asymmetric knockout of X and somatic mutation have been suggested as potential mechanisms [1] [21]. Robertson *et al.* reported monozygotic twin sisters, only one of whom had NMS [1].

Similarly, Chi Hoon Oh *et al.* described the cases of three members of the same family with NMS, who presented a different phenotypic severity despite an identical mutation of the FLNA gene. The lesional description of our case presents similarities with those of the literature. Several authors have described cases of NMS associated with omphalocele [7] and hydrocephalus [22] in male subjects as in our case [1] [3] [4]. However, the particularity of our observation concerns the diaphragmatic hernia of the liver and the age of our patient who was able to survive up to 3 years without any appropriate medical follow-up due to socio-cultural constraints, while the majority of authors described that NMS was fatal in males in all cases at most shortly after birth [1] [2] [6] [16]. Our case presents similarities to that described by Van der Lely *et al.* in an 11-year-old black boy who was the sixth child of 8 siblings of a couple of healthy and unrelated parents [7]. Neou *et al.* had described two cases of Melnick-Needles syndrome in two male patients who were children of a woman who suffered from NMS. One had minor clinical manifestations with facial features resembling that

of the mother with mental retardation and the other died at the age of 03 years from an infectious respiratory complication [10].

The issue of the management of the spectrum of disorders of the otopalatodigital syndrome in general and particularly of the NMS is not only diagnostic but also therapeutic and progressive. Therapeutic options in developing countries concern surgery for some of the malformations and pediatric follow-up in a context of precarious technical facilities.

## 4. Conclusion

Melnick-Needles syndrome is a rare condition, the diagnosis of which is suggested clinically and on imaging, but confirmed by biology through molecular genetics. For our patient, the contribution of radiography, a first-line imaging modality in cases of NMS, was limited. Whole-body CT enabled us to understand the origin of the left latero-umbilical mass and to look for other intra-thoraco-abdominal malformative abnormalities with regard to the phenotypic diversity of the disease. Our clinical case raises the issue of its diagnosis, which must be early. Unfortunately in our context because of socio-cultural constraints and the insufficiency of the technical platform, we are witnessing delays in consultation which complicate the complex management which must be multidisciplinary.

## Conflicts of Interest

The authors declare no conflict of interest.

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