

CASE REPORT

Report of two Syrian siblings with Mulibrey nanism

Tareq Al Saadi^{1,*}, Mahmoud Alkhatib¹, Tarek Turk¹, Khaled Turkmani¹, Fatima Abbas¹, and Lina Khouri²

¹Faculty of Medicine, University of Damascus, Damascus, Syrian Arab Republic, and ²Department of Pediatrics, Faculty of Medicine, University of Damascus, Damascus, Syrian Arab Republic

*Correspondence address. Faculty of Medicine, University of Damascus, Mazzeh Street, Damascus, Syrian Arab Republic. Tel: +963999567195; Fax: +963118821438; E-mail: tareq145@gmail.com

Abstract

Mulibrey (MUscle–LIver–BRain–EYe) nanism is a rare autosomal recessive disease characterized by growth failure, dysmorphic features and a wide range of abnormalities affecting multiple organ systems. This report is the first to present two cases of Mulibrey nanism affecting two siblings from Syria. Mulibrey nanism can be suspected clinically due to the distinctive features of the patients. The aim of this report is to document the presence of Mulibrey nanism in Syria and to familiarize physicians in and out of Syria with this rare disease and encourage them to develop high clinical suspicion if faced with patients with similar presentations.

INTRODUCTION

Mulibrey (MUscle–LIver–BRain–EYe) nanism is a rare autosomal recessive disease caused by mutations in the TRIM37 gene, which codes for a peroxisomal protein of unknown function [1]. Associated signs and symptoms classically include growth retardation accompanied by multiple organ abnormalities [1]. Although sporadic cases have been reported in many countries, this disorder is most prevalent in Finland with the highest number of reported cases in the world [1]. Here, we present the first known cases of Mulibrey nanism in Syria. Documentation of rare cases will familiarize physicians with these diseases and help them recognize undiagnosed cases.

CASE REPORT

The two affected siblings were born to a 35-year-old father and a 32-year-old mother who are relatives and are in their usual state of health. The family consists of three children: two females and one male. Two of these children were diagnosed with Mulibrey nanism; the third sibling was completely healthy by the time of evaluation.

The first patient, a 10-year-old female, was a product of full-term pregnancy. By 1 year of age, she was referred to the endocrinology clinic at the Children's University Hospital of Damascus to be evaluated for growth failure.

Physical examination at the present time revealed short stature, high-pitched voice and characteristic craniofacial features including triangular face, broad forehead, broad nasal root and bilateral medial pseudo-strabismus caused by bilateral epicanthial folds. Other findings included abdominal distention with mild hepatosplenomegaly, pallor, swollen lymph nodes in the neck, dilated veins on the chest wall, periorbital edema and minimal pitting edema in the lower limbs, clubbed fingers and scoliosis. The patient had normal psychomotor development.

Abdominal echography confirmed the hepatosplenomegaly and revealed moderate-volume ascites, a hepatic cyst and dilated intrahepatic bile ducts. Liver biopsy revealed focal interstitial fibrosis.

Endocrine evaluation of the patient revealed growth hormone (GH) deficiency and delayed bone age. Estimated bone age was ~6.5 years by the time of evaluation.

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Figure 1: X-ray image for the normal long bones in the lower extremities.

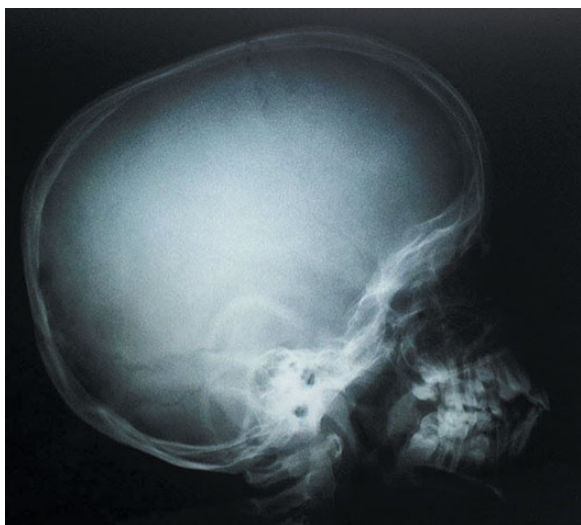


Figure 2: Lateral X-ray image for the skull showing J-shaped sella turcica.

Echocardiogram findings included the following: dilated left atrium, mitral regurgitation, tricuspid regurgitation, atrial septal defect with left to right shunt and dilatation of inferior vena cava and suprahepatic veins. The ejection fraction was within the normal range (68%). Our echocardiographic findings were compatible with restrictive left ventricular filling physiology typical of Mulibrey heart disease [2]. Constrictive pericarditis, which is part of the Mulibrey heart disease, was not discerned.

X-ray images revealed normal long and pelvic bones (Fig. 1) and a characteristic J-shaped sella turcica (Fig. 2).

Urinary system abnormalities included bilateral vesicoureteral reflux that was more prominent in the right side, hydronephrosis of both kidneys and signs of chronic renal disease in

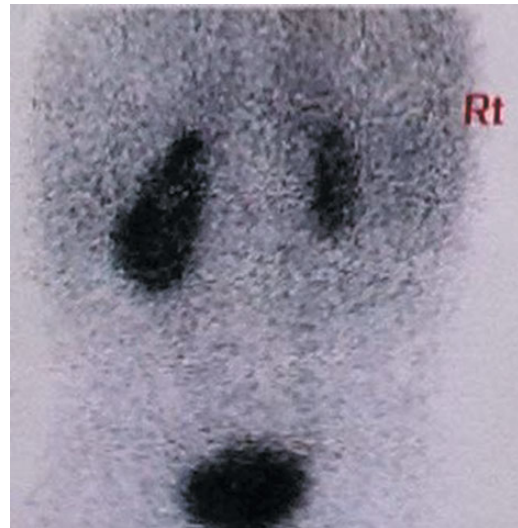


Figure 3: Renal scintigraphy showing atrophy and decreased function of the right kidney.



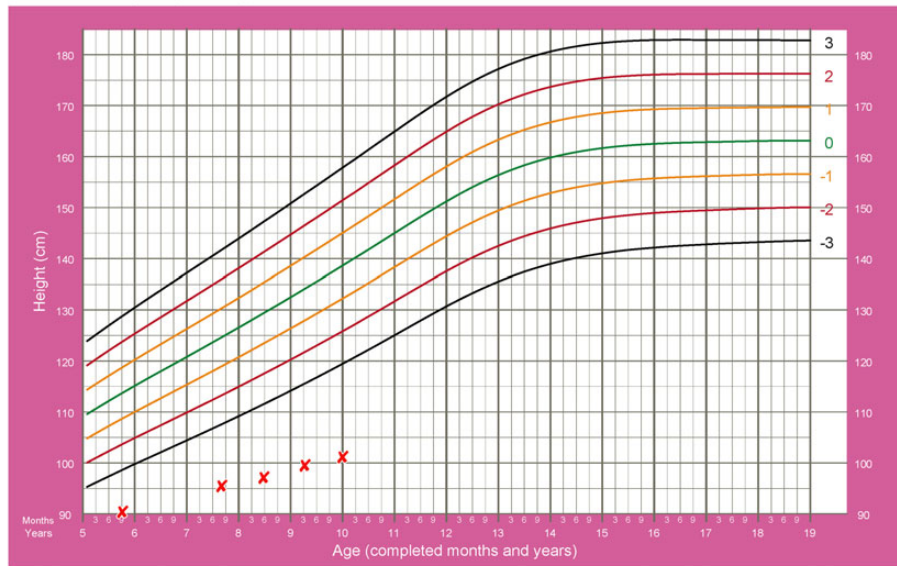
Figure 4: IVP showing Grade IV hydronephrosis in the right kidney due to ureteropelvic junction obstruction.

the right kidney, such as poor corticomedullary differentiation and cortical atrophy that were confirmed by renal scintigraphy (Fig. 3). Intravenous pyelogram (IVP) revealed right ureteropelvic junction obstruction and subsequent hydronephrosis (Fig. 4). The patient underwent ureteropelvic anastomosis and Anderson-Hynes pyeloplasty; the surgeon reported an abnormal blood vessel crossing over the right ureter, compressing it and causing the ureteropelvic junction obstruction. Three months after the surgery, reevaluation by renal scintigraphy revealed no improvement in the function of the right kidney.

Abnormal tests included elevated levels of urea, creatinine, phosphate, triglycerides, cholesterol, thyroid-stimulation hormone (TSH), parathyroid hormone (PTH), alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase

Height-for-age GIRLS

5 to 19 years (z-scores)

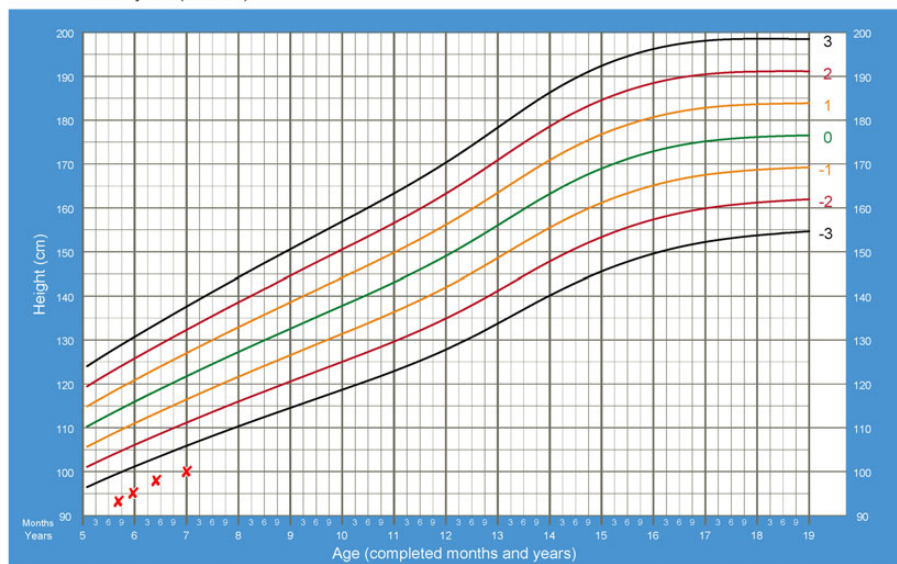


2007 WHO Reference

Figure 5: Height-for-age clinical growth chart for the first patient demonstrating the growth failure. The red marks on the chart represent measurements of the first patient's height and age obtained at each hospital visit. Growth charts are reprinted from Growth reference data for 5–19 years, height-for-age (5–19 years), World Health Organization (WHO), Copyright 2007. URL: http://www.who.int/growthref/who2007_height_for_age/en. Accessed on July 2015.

Height-for-age BOYS

5 to 19 years (z-scores)



2007 WHO Reference

Figure 6: Height-for-age clinical growth chart for the second patient demonstrating the growth failure. The red marks on the chart represent measurements of the second patient's height and age obtained at each hospital visit. Growth charts are reprinted from Growth reference data for 5–19 years, Height-for-age (5–19 years), World Health Organization (WHO), Copyright 2007. URL: http://www.who.int/growthref/who2007_height_for_age/en. Accessed on July 2015.

(ALP). In addition, decreased levels of calcium, copper, iron and luteinizing hormone (LH) were detected.

The second patient, a 7-year-old male, also was a product of full-term pregnancy with no complications at birth. The patient had short stature and high-pitched voice with the same characteristic craniofacial features as his sibling. Psychomotor development was normal. The patient had a history of mild epistaxis over the past 2 years.

Physical examination revealed pallor, mildly clubbed fingers, small-sized testicles, diffused red papules on the right leg and abdominal distention with hepatosplenomegaly. Liver biopsy revealed normal liver parenchyma. Further investigations revealed hepatosplenomegaly with a hepatic cyst and a cortical cyst in the right kidney.

Endocrine evaluation was identical to that of the first patient, with an estimated bone age of 5.5 years. Findings of the

Table 1: Diagnostic signs for Mulibrey nanism and the diagnostic findings in each of the two patients

| Signs | Patient 1 | Patient 2 |
|---|-----------|-----------|
| Major signs | | |
| Growth failure (A or B or C) | | |
| (A) Small for gestational age (SGA) lacking catch up growth | | |
| (B) Height in children 2.5 SDS below population mean for age | ✓ | ✓ |
| (C) Height in adults 3.0 SDS below population mean | | |
| Characteristic radiological findings (A or B) | | |
| (A) Slender long bones with thick cortex and narrow medullary channels | | |
| (B) Low and shallow (J-shaped) sella turcica | ✓ | |
| Characteristic craniofacial features | | |
| Scaphocephaly, triangular face, high and broad forehead, low nasal bridge and telecanthus | ✓ | ✓ |
| Characteristic ocular findings | | |
| Yellowish dots in retinal mid peripheral region | | |
| Mulibrey nanism in a sibling | | ✓ |
| Minor signs | | |
| Peculiar high-pitched voice | ✓ | ✓ |
| Hepatomegaly | ✓ | ✓ |
| Cutaneous naevi flammei | | |
| Fibrous dysplasia of long bone | | |

For the diagnosis, three major signs with one minor sign are required, or two major signs with three minor signs [1]. SDS, standard deviation scores.

echocardiogram were also similar to those of the first patient, in addition to a mild dilatation in the right heart chambers. Evaluation of renal function revealed no abnormalities.

The patient did not have a J-shaped sella turcica. However, dilated foramen magnum and signs of sphenoid sinusitis were observed. He had elongated prothrombin time (PT) and elevated levels of AST, α 1-antitrypsin (A1AT), adrenocorticotrophic hormone (ACTH) and follicle-stimulation hormone (FSH).

Height and weight at birth were not available for neither patient. However, they were measured several times during childhood. Height of both patients was >3.0 standard deviation scores below population mean for children of the same age (Figs 5 and 6). Both patients were prescribed GH replacement therapy, and diuretics were used to manage the ascites.

DISCUSSION

Most cases of Mulibrey nanism are distributed in Finland with an incidence rate of 1/37000 [3]; hence, there are physicians familiar with the disease. However, low incidence in other countries makes it challenging to recognize and diagnose Mulibrey nanism.

Unlike what the name implies, signs and symptoms of Mulibrey nanism are not limited to those four organs. Karlberg et al. described the clinical features of 85 affected Finnish patients and suggested clinical diagnostic criteria (Table 1) [1], and many other studies reported diverse clinical presentations. Genetic analysis for our patients could not be performed due to lack of proper laboratory services in Syria, and the diagnoses were made based on the phenotype of the patients meeting enough clinical diagnostic criteria.

Chronic kidney disease in the first patient was the most dangerous complication. It was caused by chronic hydronephrosis due to an abnormal vessel compressing and obstructing the right ureteropelvic junction. Although surgical management was performed, the affected kidney failed to recover. Late diagnosis and decreased health-care quality may have contributed to that unfortunate consequence. Urinary tract anomalies are common congenital malformations. Chronic kidney disease has not been reported in the context of Mulibrey nanism before. The complication was not likely caused by the mutated gene but

appears secondary to the compression of an abnormal vessel. Vascular anomalies are in itself often encountered in Mulibrey nanism [4].

Classically, cardiac involvement is the most feared complication due to its effect on life expectancy [2]. Our patients had no signs of thickened pericardium but presented echocardiographic evidence of diastolic dysfunction and valvular insufficiency, as well as hepatosplenomegaly and ascites, all signs of myocardial restriction in Mulibrey heart disease. Repeated cardiac examinations are recommended in order to detect constrictive pericarditis and restrictive cardiomyopathy. Screening for certain types of tumors, such as Wilms' tumor and benign tumors of the liver, is also important due to their large association with this syndrome [4].

Poor technological capabilities in the field of genetic analysis in developing countries, including Syria, may limit the chances for definite diagnosis of rare genetic conditions like Mulibrey nanism. We believe that reports of new cases would familiarize physicians in and out of Syria with this rare disease and encourage them to consider it when faced with patients who are having similar presentations.

CONFLICT OF INTEREST STATEMENT

None declared.

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