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Case report

X-linked spinal muscular atrophy (SMAX2) caused by *de novo* c.1731C>T substitution in the *UBA1* gene

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Abstract

Infantile X-linked spinal muscular atrophy (SMAX2) is a rare form of spinal muscular atrophy manifesting as severe hypotonia, areflexia, arthrogryposis, facial weakness and cryptorchidism, and frequently accompanied by bone fractures.

We present a male patient with SMAX2 who presented with typical symptoms at birth, preceded by reduced fetal movements in the second and third trimesters of pregnancy. Clinical examination revealed a myopathic face with a characteristic tent-shaped open mouth, tongue fibrillations, profound muscle weakness, areflexia, multiple contractures, mild skeletal abnormalities and cryptorchidism. In the first days of the patient's life, fractures of the right femur and right humerus were found; however, calcium–phosphate metabolism and densitometric examination were normal. Molecular analysis revealed a *de novo* c.1731C>T substitution in the *UBA1* gene, which was localized in exon 15, the specific hot spot for mutation.

Keywords: SMAX2; *UBA1* gene; Arthrogryposis; Hypotonia; Arflexia; Congenital fractures

1. Introduction

X-linked infantile spinal muscular atrophy (SMAX2, OMIM 301830) is a very rare, severe variant of infantile SMA. Clinical symptoms are present from birth and include signs typical for the classic *SMN1*-dependent form of SMA, i.e. hypotonia, areflexia, profound weakness and some unusual features such as a myopathic face, cryptorchidism, severe congenital contractures and bone fractures. The prognosis is poor, with most children dying within the first few months of life due to respiratory insufficiency.

SMAX2 is caused by mutation of the *UBA1* (*ubiquitin-like modifier-activating enzyme 1*) gene [1,2]. This is located on chromosome Xp11.23 and encodes the 1058-amino-acid UBA1 protein which catalyses the first step in the activation of the ubiquitin proteasome pathway (UPP). This pathway is one of the most important cellular systems which regulates degradation and modulation of proteins [3]. The discovery of ubiquitin-mediated protein degradation was awarded the Nobel Prize in Chemistry 2004.

In 1995 Kobayashi et al. linked this form of infantile spinal muscular atrophy to chromosome Xp11.3-q11.2 [4]. In 2008 Ramser et al. determined that mutations of the *UBA1* gene, located within this region of chromosome X, are responsible for SMAX2. To date, only four variants of the *UBA1* gene have been reported in six SMAX2 families, all of them localized in exon 15 [1,5].

Here we present a Caucasian patient of Polish origin with a clinical diagnosis of SMAX2 confirmed by molecular analysis.

2. Case report

2.1. Clinical picture

This male child (Fig. 1) of unrelated, healthy parents was born at 38 weeks by Caesarean section, performed due to breech presentation. Family history of neuromuscular disease was negative; both parents have healthy children from other relationships (Fig. 2). Reduced fetal movements were observed in the second half of pregnancy, but serial ultrasound scans did not demonstrate a reduction in amniotic fluid volume or abnormalities in fetal morphology. The patient's birth weight was 3150 g (25–50 c), length −57 cm (25–50 c), head circumference −38 cm (97 c) and Apgar score 8/8/8 points at minutes 1, 5, and 15, respectively. After birth, facial dysmorphy, weak cry, joint contractures and weak spontaneous

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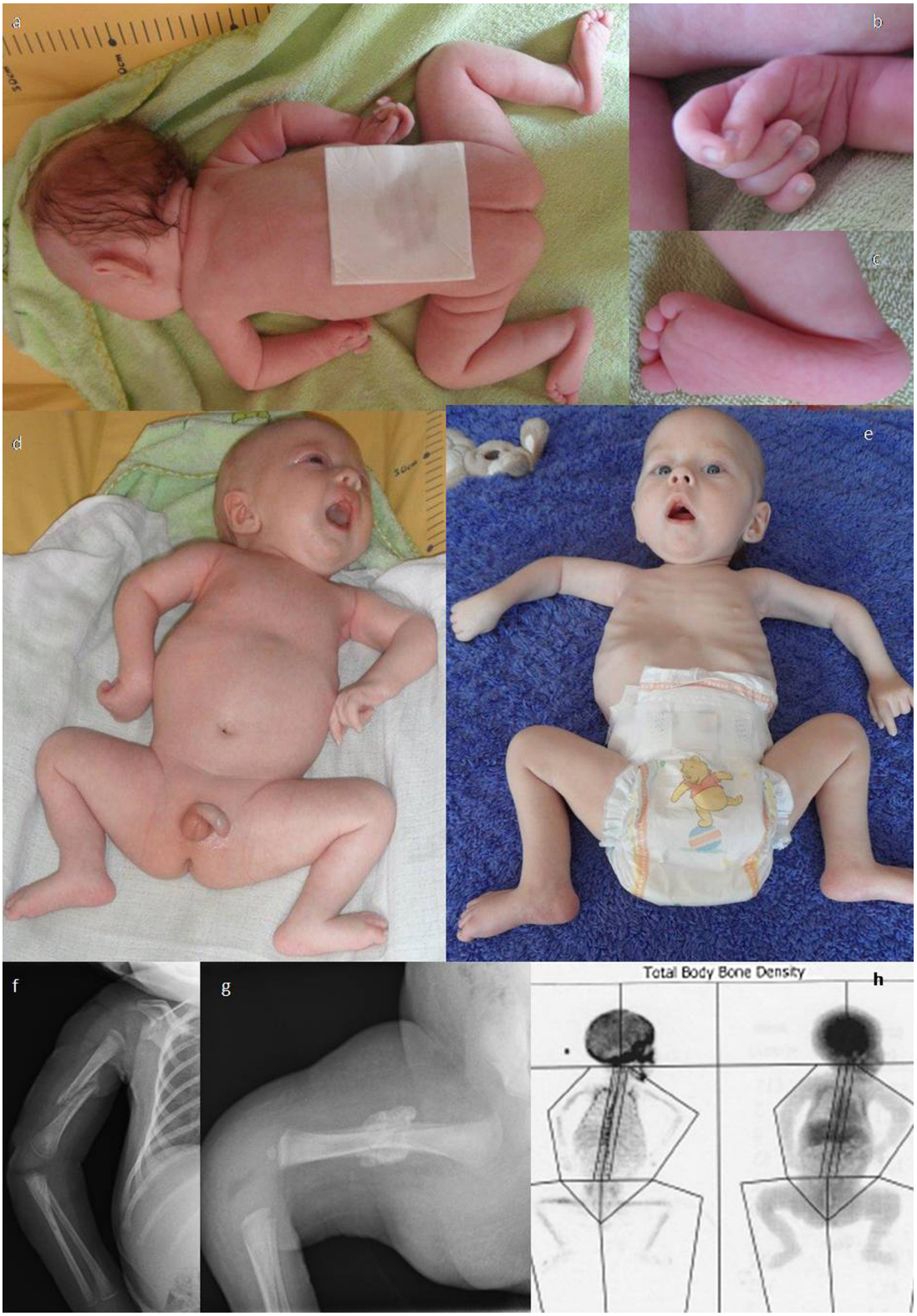

Fig. 1. (a–c) The patient after birth. Flexion contractures in hips, knees, ankles, shoulders, elbows, wrists and fingers are observed. Note contractures of internal rotators of the shoulder giving a "jug-handle" posture of arms, typical for the very severe form of *SMN1*-dependent SMA. (d) The patient at the age of six weeks. Contractures and week spontaneous movements are still present. Testes are undescended. (e) The patient at the age of 5 months. Note good eye-contact but poor facial expression with tent-shaped mouth. Movements are restricted to proximal parts of the upper limbs. Contractures are milder but still present. Fingers are flexed, with difficulty opening the hands. The chest is wide, non typical for severe *SMN1*-dependent SMA (f) X-ray showing the right humeral fracture. (g) Healing fracture of the right femur (19th day of life). (h) Densitometry; Infant Programme, TBLH (total body less head) 0.273 g/cm$^{2.}$

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