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CASE REPORT

Mowat–Wilson syndrome: the clinical report with the novel mutation in ZFHX1B (exon 8: c.2372del C; p.T791fsX816)

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Abstract
Introduction Mowat–Wilson syndrome is a congenital syndrome caused by a defect of the transcriptional repressor ZFHX1B (SIP1) gene on the chromosome 2q22–q23. The genotype–phenotype analysis confirmed that ZFHX1B deletions and mutations result in a recognizable facial dysmorphism with a multiple congenital anomaly and mental retardation.
Case report This report is about one new patient from Croatia with the typical phenotype. Molecular genetic studies showed the novel mutation in ZFHX1B (exon 8: c.2372del C; p.T791fsX816). This mutation has not been reported before. The literature is reviewed.
Conclusion Mowat–Wilson syndrome is a newly described congenital syndrome and should be considered in any individual with characteristic facial features and mental retardation in associations with congenital malformations.

Keywords Mowat–Wilson syndrome · Congenital syndrome · Hirschsprung disease · Seizures · Mental retardation · ZFHX1B gene

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Introduction

In 1998, Mowat et al. identified among six sporadic patients with "syndromic Hirschsprung disease" (HSCR) a locus at the chromosome 2q21–q23. Those patients had distinct facial phenotype, microcephaly, mental retardation, and HSCR (Hirschsprung disease). Three years later, Wakamatsu et al. reported mutations in ZFHX1B in patients with syndromic HSCH, and Cacheux et al. proved the same mutations in patients previously reported by Mowat. HSCR has not been an obligatory symptom in all the patients with proven mutation, so Zweier et al. suggested that Mowat–Wilson syndrome (MWS) is a more appropriate name. The patients with deletions were very similar to those with truncating mutations. There was no correlation between the phenotype and size of deletion up to 5 Mb (one patient with a larger deletion had early seizures with a lethal course) [6, 8, 12].

The incidence of MWS is unknown, but to date, over 100 cases with proven mutation were reported [1, 3, 12], and all reports show a striking resemblance of the facial features and uniformity of the associated malformations. In most patients, main facial features were present (hypertelorism, epicanthus, high broad forehead, broad nasal bridge, small nose with round tip, open mouth, prominent chin, and posterior low-set ears with uplifted lobes) [2, 8].

The mental retardation was constant; other malformations were reported in variable frequency such as HSCR, heart defects, agenesis of corpus callosum, seizures, genitourinary malformations, and microcephaly. The male/female ratio is from 2.13:1 [2] to 1:1 in latest studies [1, 3].

This report represents the clinical data of a child from Croatia with the typical phenotype and with the mutation in ZFHX1B.

Clinical report

This 5-year- and 8-month-old boy, born in 1998, is the first child of healthy nonconsanguineous parents. Family history was negative for any congenital anomalies. He was born at 40 weeks gestation with a birth weight of 2,520 g (p=5), length of 46 cm (p=5), and head circumference of 32 cm (p<5).

On birth, he showed distinct malformations, and the following was observed: hypertelorism, epicanthus, strabismus of the right eye, posterior low-set ears, hypoplastic nasal bridge, hearth murmur, hypospadia, cryptorchidism of right testis, dermatoglyphic anomalies, evident opistotonus, and muscle hypertonia. Tests were performed: Karyotyping was normal; ophthalmoscopic tests showed fundus tabulatum. Visual evoked potentials after "flash" stimulation showed dysfunction of both visual pathways. Electroencephalogram (EEG) showed delayed cerebral maturation. In that time, all tests and observations did not lead to any conclusion about the boy's disorder.

When he was 18 months old, febrile seizures started, repeatedly with every upper respiratory infection and recurrent otitis media up to the age of 5 years when attacks occurred without fever, almost every day in initial phases of sleeping. The combined antiepilepsy therapy (Na valproat, phenobarbitone, and lamotrigine) had poor effect on seizures frequency. He started to walk when he was 30 months old, but for a long time, he needed parental support or holding on to the furniture.

In our clinic (The Referent Centre for Epilepsy), he was presented for the first time at 5 years and 8 months of age because of uncontrolled epilepsy.

Upon our examination, the following characteristics were observed: weight, 18 kg (p=10–25); height, 113 cm (p=50); body mass index (BMI), 14.10 (p=10); head circumference, 47 cm (p<5, 2 SD); pale skin, hypertelorism, epycanthus, broad nasal bridge, saddle nose, eyebrows broad and horizontal with wide medial separation, open mouth with hyper salivation, broad space between teeth, posterior low-set ears with uplifted lobes. He was affectionate, frequently smiling, and had no speech developed; he was walking holding on to furniture or parents. On the left palm of his hand, he had dermatoglyphic anomalies. He had on his penis a scar from reconstructive operation of hypospadia and split prepucium, undescended left testis, and agenesis of right testis. A cardiac systolic murmur was present (electrocardiogram and echocardiogram were normal). Audiometric examination was normal. Standard caryotyping was repeatedly normal; metabolic disease was excluded.

The magnetic resonance imaging of the brain showed a hypoplastic corpus callosum. EEG recording in alert state showed bilateral discharges of sharp waves and spike and wave complexes over frontal regions with secondary generalization.

The seizures had initially occurred at the age of 18 months during a febrile state. At the age of 5 years epileptic fits became more frequent.

On the last examination at 6 years and 8 months of age, the patient's weight was 20 kg (p=25), length was 121 cm (p=50), BMI was 13.66 (p=5), and head circumference was 47.5 cm (p<5, 2 SD); he is walking alone but not yet stabile, with gait wide based; his speech is restricted to few words; and he usually communicates with his mother by signing. He is taking the antiepileptic therapy (topiramate and lamotriginum), and for the last 8 months, he had no seizures.

Methods and results

Karyotyping showed repeatedly normal result.

Flourescent in situ hybridization (FISH) analysis was performed with four different bacterial artificial chromosome clones (from the ZFHX1B locus) on metaphase spreads. DNA was isolated from leucocytes prepared according to standard methods. From the sample, all coding exons (2–10) of the ZFHX1B gene was amplified by polymerase chain reaction (PCR). The amplicons were purified and directly sequenced from both directions with an ABI 3730 capillary sequencer. To confirm the detected mutation, sequencing was repeated from a second PCR amplicon. FISH analysis for gross deletions showed normal result, but sequencing of the whole coding region of the ZFHX1B showed a new heterozygous stop mutation in exon 8 within the CtBP-interacting domain (exon 8: c.2372del C; p. T791fsX816). The putative protein would show a premature translational stop, thus, missing the c-terminal zinc finger cluster.

Discussion

We report on the clinical data of a boy with the Mowat–Wilson syndrome who is now over 9 years of age. He has a de novo and not yet reported mutation in the ZFHX1B gene.

We found, in our patient, all major characteristics such as facial features, mental retardation, microcephaly, and hypoplastic corpus callosum, as well as hypospadia, cryptorhismus, and one-sided testicular agenesis. He also has optic peripapillary atrophy, fundus tabulatus, but no HSCH, cardiac anomalies, or vesicoureteral reflux.

Distinct facial appearance is, according to all authors, a leading marker: medially flaring thick eyebrows, hypertelorism, deep-set eyes, prominent pointed chin, and posterior low-set ears with uplifted lobes. Severe mental retardation and microcephaly are constant anomalies. Other major malforma-

tions are frequent but more variable: seizures, HSCH, happy affectionate personality, congenital heart disease, agenesis or hypoplasia of the corpus callosum, hypospadias and cryptorhismus, and renal anomalies [9, 13].

Zweier et al. [14] classified 70 patients into typical MWS, ambiguous, and atypical groups according to their facial phenotype without prior knowledge of their mutation status. In all 28 patients classified as typical, truncating mutations were detected. Analyzing all reported 97 cases, authors suggested that significant positive predictors of the ZFHX1B defect are agenesis of corpus callosum and urogenital anomalies (especially hypospadia in males).

In their study, a novel clinical features of MWS were observed: the structural ocular anomalies such as microphthalmia [14]. Ocular anomalies was reported previously by Gregory Evans et al. [4] (myopia and coloboma of retina and iris) and by Mc Gaughran et al. [7] (coloboma in only one siblings with MWS). Adam et al. [1] report in five cases strabismus, one patient with cataract, and one with myopia.

The peripapillary atrophy observed in our patient could eventually be a new clinical feature of MWS rather than a mere coincidence.

Adam et al. [1] propose the following criteria: a patient with developmental delay or MR and prominent nasal tip with columella in addition to at least one other distinctive facial characteristics and at least one of the following: HSCH, seizures, agenesis or hypoplasia of corpus callosum [1].

No genotype–phenotype correlation can yet be established. In a recent study, Dastot-Le Moal et al. analysed approximately 160 mutations in ZFHX1B gene reported to date. A large proportion of mutations are in exon 8, which contains 60% of the coding sequence. Small deletions/insertions in the coding sequence account for about 54% of identified mutations, causing frameshifts and producing truncated mutant protein [3]. Two independent patients had the same mutation [6 with variability in phenotype, and McGaughran reports brother and sister with difference in their clinical phenotype and the same truncating mutation in the exon 8. Nonsense mutations account for 41%, also localized mainly in exon 8, and in that, group six recurrent mutations were observed. The analysis of the clinical manifestations showed a striking phenotypic variability [3, 6, 7]. The patient in this report have a novel stop mutation in exon 8, and it has not been reported before.

Missense mutations have been described in two patients with atypical phenotypes [4, 5], one in combination with trisomy 21 and the other with cleft lip palate and brachytelephangalia. The third patient with missense mutation reported by Dastot-Le Moal had a severe clinical course, died at age 3, and had typical MWS with HSCR.

In the group of patients with splice-site mutations, Zweier et al. [14] described a patient with typical but mild facial appearance and milder developmental delay and no congenital anomalies. Mutation was in 5ÚTR, and as the author suggests, it might contain important determinations of the facial phenotype [14].

MWS is an autosomal-dominant complex development disorder, and most of the reported patients has been sporadic cases with low recurrence risk for siblings. Exception from this are two families reported up till now: McGaughran et al. published a case of a brother and a sister with MWS [7]. They both have the same truncating mutation in exon 8 of the ZFHX1B. Their parents are phenotypically normal, and the same mutation is excluded; authors suggest that the most likely explanation is germ-line mosaicism. Zweier et al. [14] observed two affected sisters, caused by low-level paternal mosaicism, born to healthy parents [10–12].

In our patient, mutation has arisen de novo; the same mutation was excluded in parents, but because of the possibility of germ-line mosaicism, prenatal diagnostics for future pregnancies has been advised to both parents.

As a MWS is a relatively newly recognised congenital syndrome, follow-up studies of patients with proven mutations are necessary to give answers to expectations of parents and therapists. Early recognition of the syndrome is important, so significant positive predictors of the ZFHX1B defect are suggested; prenatal diagnostics for future pregnancies are obligatory advise to parents, but in the future studies that will follow, those patients are required to give answers to families about medical problems to be expected. Adam et al. described two oldest patients (21 and 23 years old); they have no speaking abilities (able to sign one word), have no aggressive behaviors, and require assistance with activities of daily living [1]. Our patient today is 9 years old; facial phenotype of MWS is more pronounced: Nasal tip is more depressed; the jaw is more prominent; he is walking alone; his speech is restricted to yes and no, and with antiepileptic therapy, the seizures are well controlled.

In conclusion, MWS is a newly described congenital syndrome and should be considered in any individual with characteristic facial features and mental retardation, especially in combination with agenesis/hypoplasia of corpus callosum, HSCR, seizures, or anomalies of hearth, genitourinary defects, and ocular anomalies. We report on the clinical features of a child with MWS. Our patient has the most of already reported clinical anomalies and the proven gene defect that has not yet been found in others. With this case report, we wish to contribute to further investigations about this new and rare syndrome.

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