OPEN

Diverse clinical outcome of Hunter syndrome in patients with chromosomal aberration encompassing entire and partial IDS deletions: what is important for early diagnosis and counseling?

Aleksandra Jezela-Stanek[a], Paulina Pokora[b], Marlena Młynek[c], Marta Smyk[d], Kamila Ziemkiewicz[d], Agnieszka Różdżyńska-Świątkowska[e] and Anna Tylki-Szymańska[b]

Our study aims to delineate the syndromology of Hunter syndrome (MPSII), by presenting three patients with different clinical courses, caused by different genetic mechanisms. Single-nucleotide variants (SNV) or small deletions encompassing the iduronate-2-sulfatase (*IDS*) gene are identified in the majority of affected individuals, while deletion of contiguous genes or whole *IDS* gene (described herein) has been reported rarely, mainly in patients with a severe Hunter syndrome presentation. There is; however, lack of reliable genotype–phenotype correlation, especially regarding anthropometric parameters, and thus our understanding of MPSII pathophysiology is not complete. On the basis of our observations, we would like to draw attention to the fact that neurological manifestations observed in patients with contiguous gene deletions, encompassing the *IDS* gene, may significantly differ from those observed in SNV. The phenotype is; however, difficult to predict and depends on the type (deletion/duplication), size (small/large) of aberration, and gene content. Moreover, it also has implications for genetic counseling, and recurrence risk in those families differs from the usual situation and must be clarified by parental chromosomal studies. *Clin Dysmorphol* 30: 76–82

Clinical Dysmorphology 2021, **30**:76–82

Keywords: chromosomal deletion, hunter syndrome, *IDS* gene, *IDS-2* pseudogene chromosomal aberrations, mucopolysaccharidosis type II

[a]Department of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Disease, [b]Department of Paediatric, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute, [c]Department of Medical Genetics, The Children's Memorial Health Institute, [d]Department of Medical Genetics, Institute of Mother and Child and [e]Anthropology Laboratory, The Children's Memorial Health Institute, Warsaw, Poland

Correspondence to Anna Tylki-Szymańska, Department of Paediatric, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland
Tel: +48228157584; fax :+48228157489; e-mail: a.tylki@ipczd.pl; atylki@op.pl

Received 9 September 2019 **Accepted** 26 May 2020

Mucopolysaccharidosis type II (MIM #309900), also known as Hunter syndrome, belongs to the group of lysosomal storage disorders and is caused by a deficiency of iduronate-2-sulfatase (I2S, IDS), which results in storage of heparan and dermatan sulfate (Neufeld and Muenzer, 2001). The primary causative defect lies in mutations in the *IDS* gene, located on chromosome Xq28 (Hopwood *et al*., 1993). In the majority of affected boys single-nucleotide variants or small deletions are identified (Froissart *et al*., 2007; Scarpa, 2018), while deletion of contiguous genes or the whole *IDS* gene has been reported mainly in patients with severe Hunter syndrome presentation (Brusius-Facchin *et al*., 2012; Zanetti *et al*., 2014; Vollebregt *et al*., 2017).

Patients diagnosed with partial or entire *IDS* gene deletions presented neuronopathic, severe phenotype (Gort *et al*., 1998; Brusius-Facchin *et al*., 2012; Zanetti *et al*., 2014; Vollebregt *et al*., 2017). There is; however, a lack of reliable genotype-phenotype correlation, especially regarding anthropometric parameters, and thus our understanding of molecular pathology is not complete. In this article, we present two individuals carrying chromosomal aberrations, and a further patient with partial deletion encompassing *IDS* gene, whose mucopolysaccharidosis type II (MPSII) was rather mildly expressed but with significant developmental delay (unusual even for severe Hunter syndrome).

We present molecular data and draw attention to the fact that neurological manifestations should not be defined as severe mucopolysaccharidosis as such, but rather classified as MPS as part of a chromosomal aberration where the phenotype results from the type (deletion/duplication) or size (small/large) of the aberration and of the gene content.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, http://www.clindysmorphol.com.

0962-8827 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. DOI: 10.1097/MCD.0000000000000344

Case presentation

Medical histories with diagnostic results of the three presented probands are shown in Table 1. Both patients with a chromosomal deletion, including the entire *IDS* gene, came to medical attention because of profound developmental delay. In patient 1, karyotyping was performed when he was 6 months of age (because of unspecific facial dysmorphism; parents gave no consent for photographs), while in patient 2 (diagnosed with Hunter syndrome at the age of 7 years), a cytogenetic test was performed because of neurodevelopmental delay.

Patient 3, diagnosed with pathogenic rearrangement between the *IDS* gene and *IDS-2* pseudogene, presented developmental delay as well, but – notably – not as severe as the other two patients, and unlike them, he had no hearing disability. His chromosomal analysis was normal. His phenotype; however, was very suggestive of storage disorders (distinctive facial coarseness, umbilical hernia, skeletal anomalies with joint contractures, together with hepatosplenomegaly and ventriculomegaly) already at the age of 2 years.

Methods and results

All diagnostic procedures were approved by the probands' legal guardians and done following ethical principles.

Array comparative genomic hybridization (array-CGH) was performed on DNA extracted from peripheral blood cells of patients by using commercially available arrays (patient 1 – CytoSure, ISCA 8×60 K v2.0, Oxford Gene Technology, Oxfordshire, UK; patient 2 – SurePrint G3 ISCA V2, 8×60 K, Agilent Technologies, Santa Clara, USA), according to the manufacturer's protocol.

In patient 1, array-CGH showed a duplication of ~1.1 Mb in chromosomal region 8p22 encompassing exons 2–8 of *SGCZ* gene [arr 8p22(13468298_14572671)×3] (Fig. 1a) and an interstitial deletion of ~9.27 Mb of Xq27.2q28 [arr Xq27.2q28(140414526_149682984)×0] (Fig. 1b) [University of California at Santa Cruz (UCSC) Genome Browser; build hg19, March 2006] including 23 OMIM genes: *AFF2*, *CXorf40A*, *FMR1*, *IDS*, *MAGEA11*, *MAGEA8*, *MAGEA9*, *MAGEA9B*, *MAGEC1*, *MAGEC2*, *MAGEC3*, *MAMLD1*, *SLITRK2*, *SLITRK4*, *SPANXA1*, *SPANXA2*, *SPANXD*, *SPANXN1*, *SPANXN2*, *SPANXN3*, *SPANXN4*, *TMEM185A*, and *TMEM257*. Four of these genes are OMIM morbid (*AFF2*, *FMR1*, *IDS*, and *MAMLD1*, Table 2, supplement digital content 1, *http://links.lww.com/CD/A14*). Additionally, the Xq27.2q28 deletion encompassed seven non-OMIM genes: *CXorf40B*, *CXorf51A*, *CXorf51B*, *FMR1NB*, *HSFX1*, *HSFX2*, and *UBE2NL*. Telomeric end of the deletion is located ~50 kb from *MTM1* gene.

In patient 2, array CGH revealed an approximately ~2.11 Mb hemizygous deletion within Xq27.3q28 [Xq27.3q28(147089971_149204436)×0; hg 19] (Fig. 2). The deleted region encompassed nine OMIM genes: *AFF2*, *IDS*, *CXorf40A*, *MAGEA9*, *MAGEA9B*, *TMEM185A*, *MAGEA11*, *LINC00850*, and *MAGEA8*, two of them (*AFF2*, *IDS*) are OMIM morbid (Table 2, supplement digital content 1, *http://links.lww.com/CD/A14*). In addition, there were 9 non-OMIM genes (*FMR1NB*, *LINC00893*, *HSFX3*, *HSFX4*, *HSFX2*, *HSFX1*, *MAGEA8-AS1*, *CXorf40B*, and *LINC00894*) within the deletion. Further microarray investigation showed that the same deletion was present in the mother of the patient.

Analyses of the *IDS* gene (PCR and gel electrophoresis) in Patient 3 were performed in Centogene AG (Rostock, Germany) and revealed hemizygous pathogenic rearrangement between intron 3 and intron 7 of the *IDS* gene and *IDS-2* pseudogene.

Anthropometry

Measurements of weight, height, and head circumferences of our patients are presented in Figs. 3 and 4. They concern data at the age of 0–36 months for patients 1 and 3, 0–8 years for patient 2.

Discussion

Hunter syndrome manifests with a recognizable clinical picture but with a wide range of severity. At the clinically most severe presentation, it shares many features with Hurler syndrome (MPS I, OMIM 607014), the most severe type of mucopolysaccharidosis I. These may include abnormal facial appearance (full cheeks, low nasal bridge, anteverted nostrils, broad nasal tip, full lips, and hypertrophy of alveolar ridge), thoracolumbar Gibbus (evident by 4–6 months of age), hepatosplenomegaly, cardiovascular disorders due to mucopolysaccharide deposits (Kampmann *et al.*, 2011), dysostosis multiplex with short stature, hypoacusis, and neurocognitive delay (evident by 12–24 months of age) (Wraith *et al.*, 2008; Burton and Giugliani 2012). The latter refers especially to male patients with the complete absence of functional enzyme as a result of gene deletion or complex gene rearrangements (~17% of affected individuals), who invariably manifest the early progressive central nervous system (CNS) presentation of the disease (Wraith *et al.*, 2008).

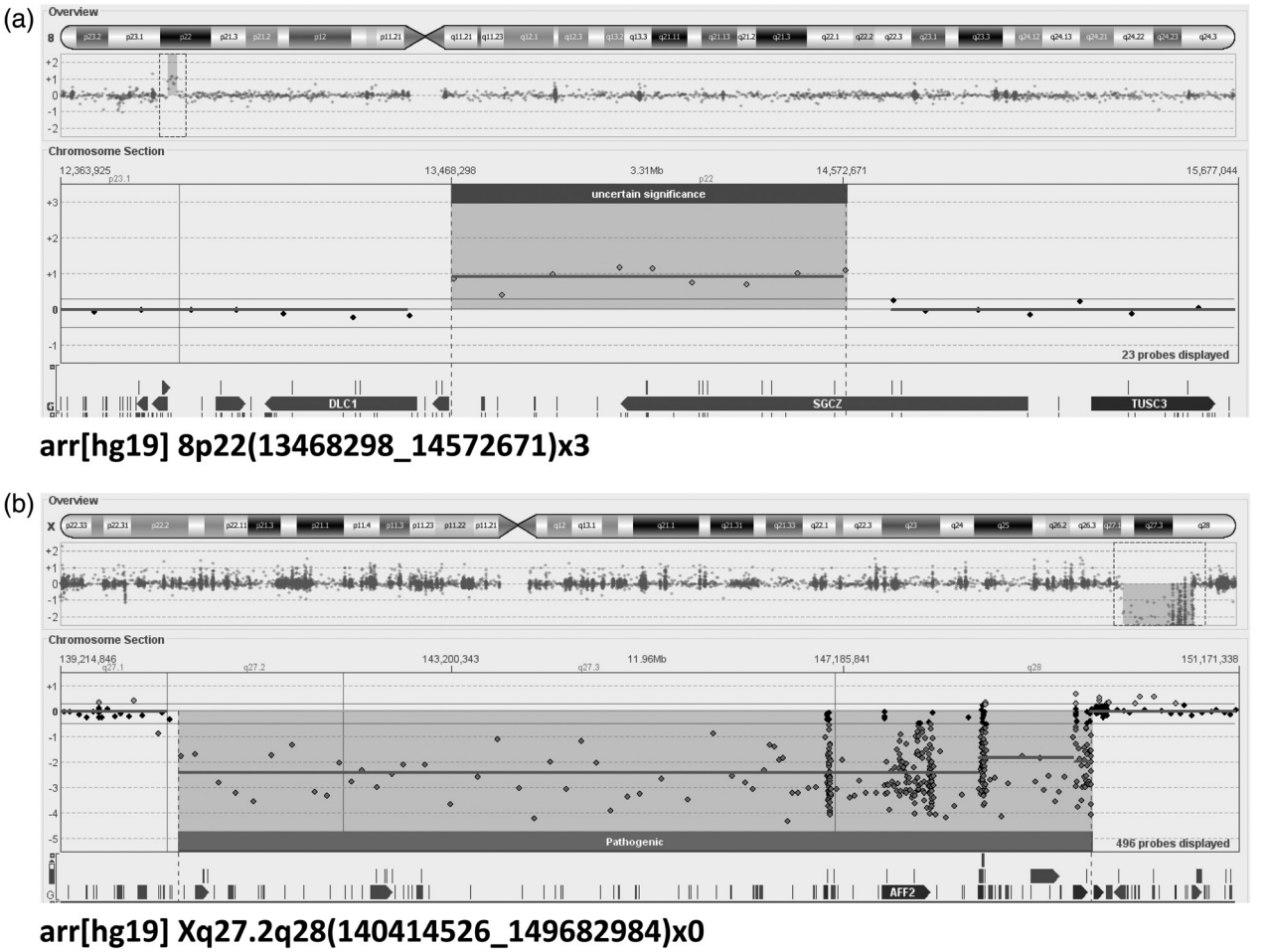
The progression rates in Hunter syndrome vary between affected individuals and this is evident in patients 1 and 2. Both these probands were referred to genetic counseling because of developmental delay and unspecific facial dysmorphism. Thus, the diagnostic tests were started with chromosomal analysis. These allowed for the identification of complex chromosomal rearrangements, encompassing the deletion of the entire *IDS* gene (Figs. 1 and 2). In both boys, MPS was ultimately confirmed. The only physical features that drew attention toward lysosomal storage disorders (LSDs) were a combination of lumbar kyphosis, large tongue, and hernias, with a history of recurrent otitis media/hearing loss in patient 1. In patient 2, phenotypic manifestation was more severe and joint contractures developed during early childhood. Recognition of Hunter syndrome in early childhood

Table 1 Remarkable clinical features and laboratory results observed in our individuals

	Patient 1	Patient 2	Patient 3
	Entire *IDS* deletion as a result of chromosomal aberrations		Partial *IDS* deletion as a result of recombinations with *IDS* pseudogene
History			
Pregnancy	GI, birthweight 3360 g, 10 points in Apgar scale	GII (pelvic position), PII (cesarean section), 38 weeks of gestation, birthweight 3600 g, length 58 cm, OFC 37 cm (sagittal suture widened, coronal suture thickened) chest 33 cm, 7–9 Apgar scale, symptoms of hypoxia	GIIIPIII (cesarean section), 38 weeks of gestation, birthweight 3200 g, length 52 cm, OFC 35 cm chest 33 cm, 8–10 Apgar scale
Neonatal period	Bilateral hypoacusis, laryngomalacia recurrent upper and lower airway infections, and otitis media (which continue through infancy and early childhood)		Physical abnormalities (retrognathia, high palate, short neck, short clavicles, and long bones: fumerus, femur; but no objective data are available) hypoglycemia, prolonged jaundice
Infancy	Apnea episodes (no congenital heart disease) bilateral inguinal hernia significant developmental delay (no sitting, crawling, walking, head control, and speech ability)	Hydrocephalus, ventriculoperitoneal valve implantation (6 m) bilateral inguinal hernia (12 m – surgery correction) significant developmental delay (sitting and crawling 12 months, getting up 2 years, in 4 years he stopped to get up)	Ventriculomegaly with asymmetry developmental delay
Childhood	From 3 years: rolling over slow growth rate severe DD	Slow growth rate severe DD/ID with lack of verbal communication sensorineural hearing loss recurrent upper and lower airway infections	Hepatosplenomegaly otitis media
Physical abnormalities	Thick infiltrated skin, pectus carinatum, short lower limbs, thoracolumbar kyphosis, axial and peripheral hypotonia, contractures of the knee joints, stiffness of the shoulder girdle with limited abduction and bending, liver and spleen within normal limits	Contractures in the joints of the upper and lower limbs, thoracolumbar kyphosis, short stature (<3c), liver and spleen within normal limits	Pectus carinatum, thoracolumbar kyphosis, umbilical hernia, contractures in the joints of the upper and lower limbs
Craniofacial dysmorphic features	OFC: 90–97 c, and increased head length enlarged tongue, swollen eyelids, broad nostrils	OFC >97 c, increased sagittal head length, enlarged tongue	OFC >97c distinctive coarseness: prominent forehead, short nose with flat nasal bridge, full lips
Diagnostic tests			
Karyotype	46, der(X)Y, further molecularly defined as Xq28 deletion (at age 6 months)	Not performed	Not performed
CMA	8p22(13468298_14572671) × 3,Xq27 .2q28(140414526_149682984) × 0	Xq27.3q28(147089971_149204436) × 0 (maternally inherited)	Normal
uGAGs/GAGs	127.37 mg/mmol creatinine [ref. for age 6–12 months: 16. 45–32.45] (at age 9 months)	96.0 mg/mmol creatinine [ref.: 5.78–13,2] (at age 7 years) GAGs electrophoresis: dermatan sulfate, heparan sulfate	111.0 mg/mmol creatinine [ref.: 5.88–23.0] (at age 2 years)
IDS gene	NGS, MLPA: hemizygous deletion encompassing the whole *IDS* gene	NGS, MLPA: hemizygous deletion encompassing the whole *IDS* gene	PCR: hemizygous pathogenic rearrangement between intron 3 and intron 7 of the *IDS* gene and *IDS-2* pseudogene
Iduronate-2-sulfatase (ref.: ≥ 5.6 µmol/L/h)	<0.8 (LOD) µmol/L/h	<0.8 (LOD) µmol/L/h; 0,01 (ref.: 354 ± 86) [α-L-iduronidase: 81 µmol/L/h (ref.: 129 ± 40)]	<0.8 (LOD) µmol/L/h
Age of MPSII diagnosis	9 months	7 years	2 years
Clinical course	The patient has developed with significant delay. His clinical history was also marked by recurrent airway and middle-ear infections. He has been treated with ERT (for almost 2 years but with no clinical effect. The boy died at the age of 3 (soon after ERT was ended).	The patient's development from the beginning proceeded with a significant delay. He remained mainly under neurosurgical care due to frequent revision and reimplantation of the ventricular and peritoneal valve. It was not until the seventh year that suspicion of mps and the diagnosis was made (enzymatic and molecular tests). In view of the atypical course, mainly in the form of severe intellectual disability, the diagnosis was extended by the CMA study and confirmed the deletion of a fragment of the long arm of the X chromosome including, in addition to the *IDS* gene, among others the *FRAXE* gene. The patient is waiting for ERT.	Beckith–Wiedemann syndrome was excluded
Additional tests/other abnormalities		Heart ultrasound: thickened mitral and tricuspid valve flap, low regurgitation	

CMA, chromosomal microarray; DD/ID, developmental delay/intellectual disability; ERT, enzymatic replacement therapy; LOD, limit of detection; MLPA, multiplex ligation-dependent probe amplification; MPSII, mucopolysaccharidosis type II; NGS, next-generation sequencing; OFC, occipitofrontal circumference; uGAGs, urinary glycosaminoglycans.

Fig. 1



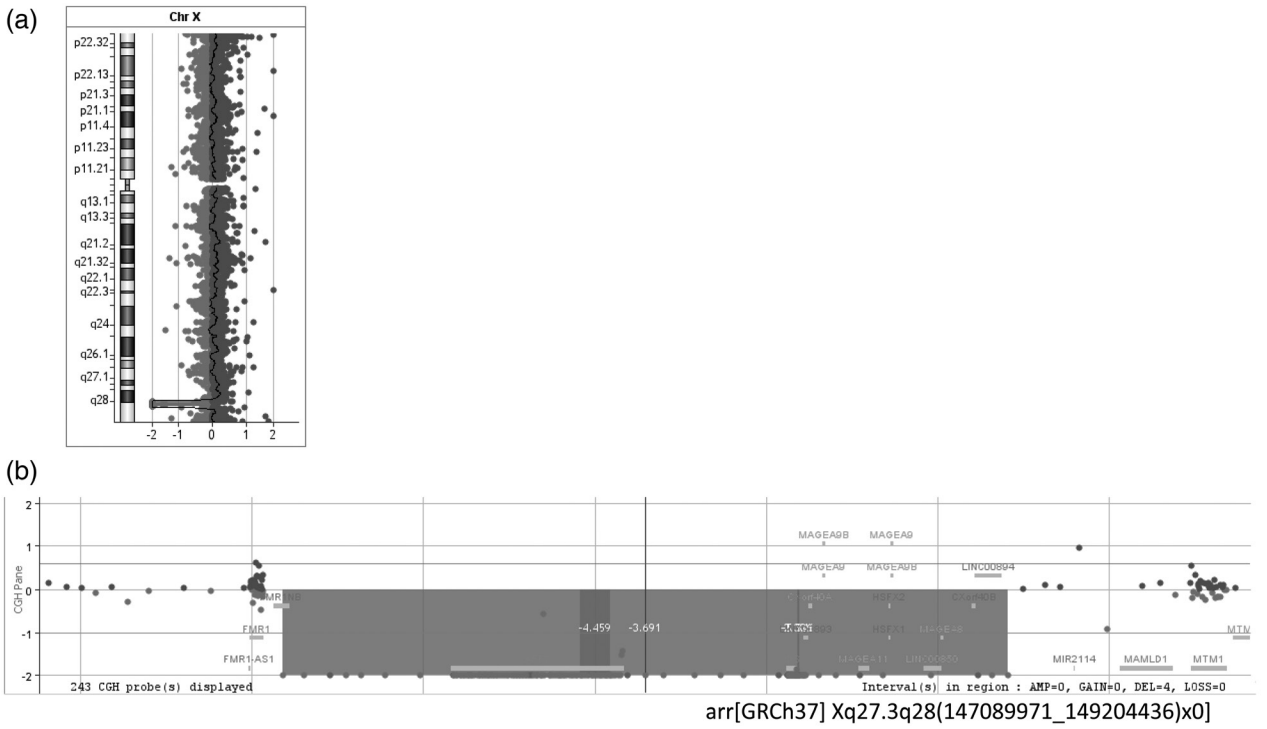
Partial array-CGH results, focusing on the 8p22 duplication (a) and the Xq27.2q28 deletion (b) that is present in patient 1. CGH, comparative genomic hybridization.

requires really careful attention and experience, especially with the subtle facial features.

Compared to other cases with *IDS* deletion and complex chromosomal rearrangement from the literature, in patient 1 we did not observe: hydrocephalus, obstructive pulmonary disorder, and pulmonary hypertension (Brusius-Facchin *et al.*, 2012), claw hands, hepatosplenomegaly (Zanetti *et al.*, 2014). His clinical course was; however, definitely severe, marked by profound neurodevelopmental delay and congenital hypoacusis. The clinical course must be influenced by aberrations within other genes (Table 2, supplement digital content 1, *http://links.lww.com/CD/A14*): for example, in patient 1 deletion of *FMR1*, and in patient 2 deletion of the *FMRE* gene. Several other deleted or duplicated genes are concerned but it is difficult to attribute causation.

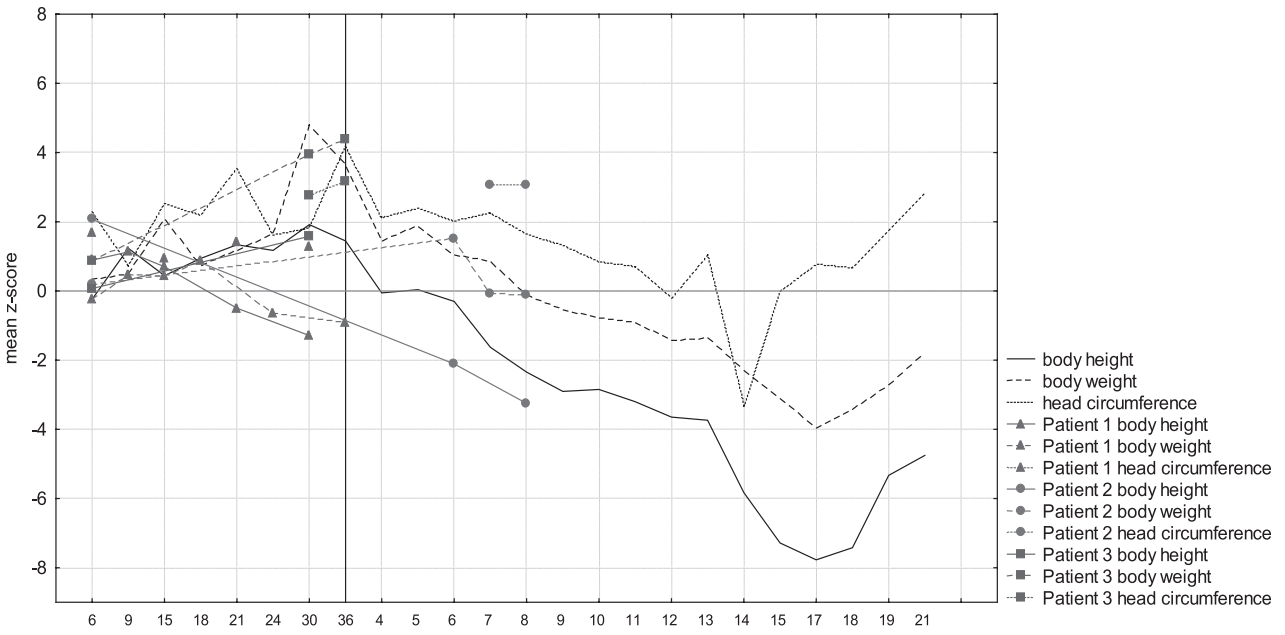
In contrast to patients 1 and 2, patient 3 presented with marked physical features of MPS II. Because of developmental delay he underwent chromosomal testing, to exclude Beckwith–Wiedemann syndrome (because of umbilical hernia), which revealed no anomalies. On the basis of clinical suggestions, further tests to identify MPS disorders were undertaken and led to the identification of recombination between the *IDS* gene and *IDS-2* pseudogene. Bondeson *et al.* (1955) firstly characterized the *IDS* pseudogene, located approximately 25 kb telomeric to the functional gene. The authors suggest that at least intron 2, exon 3, and the 3′-half of exon 2 of the functional *IDS* gene are present in the human genome as part of a nonexpressed *IDS* gene, called a pseudogene. Its 96% homology with intron 7 of the *IDS* gene, explains the susceptibility to complex recombination events. This mechanism is the cause of disease in an estimated 13% of the Hunter syndrome patients (Bondeson *et al.*, 1995).

Fig. 2



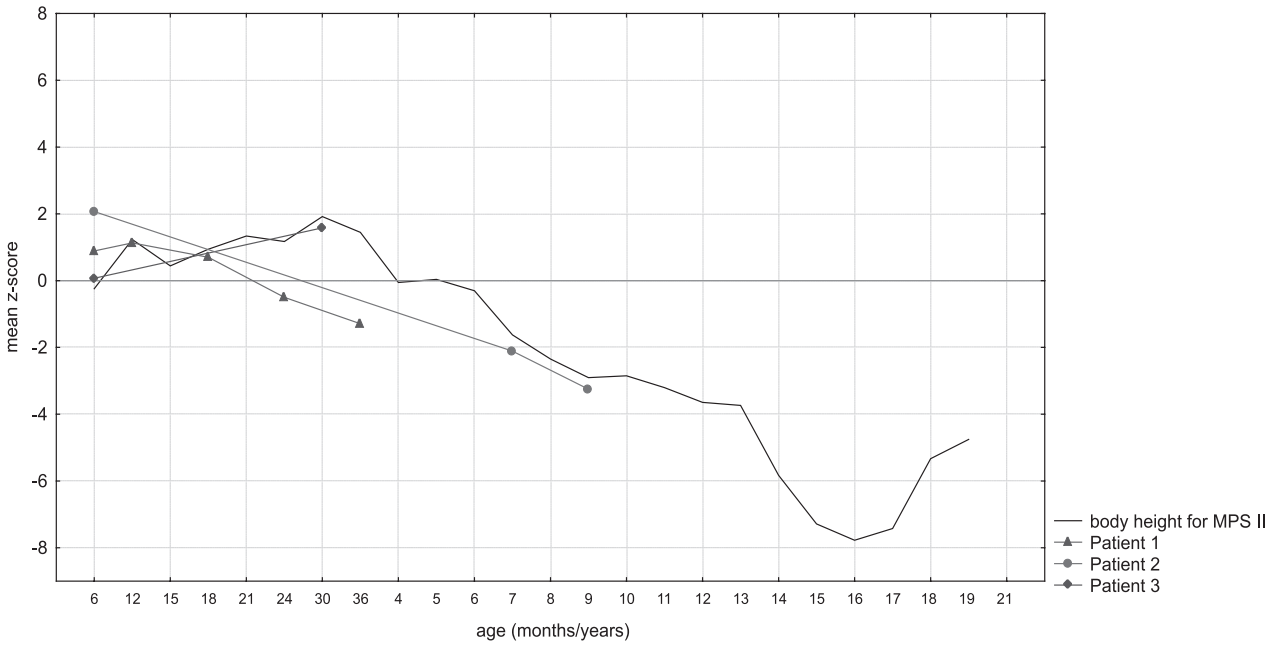
A microarray result showing the hemizygous deletion on the X chromosome in patient 2 (a) and graphic representation of part of Xq27.3q28 including the deletion area and genes contained in this region (b).

Fig. 3



Anthropometric parameters concerning height, weight, and head circumference of patients 1, 2, and 3.

Fig. 4



Height of patients 1, 2, and 3.

In this latter situation, we would like to point out that developmental delay, which otherwise is not a characteristic of MPSII, is observed and thus it is not limited to chromosomal aberrations resulting in complete *IDS* deletion. Moreover, the mucopolysaccharidosis presentation in such cases may be even more striking and recognizable, leading to an earlier diagnosis. We do agree with the general conclusion stated by Vollebregt *et al.* (2017) that the *IDS* gene deletion primarily causes the CNS phenotype in patients with MPSII. Otherwise, the clinical course may be atypical (like in our patients 1 and 2). Thus, in every patient with features suggestive LSDs but with a neurodevelopmental disorder, chromosomal aberration should be excluded (in microarray analyses). In every child with a proven aberration, physicians should be cautious with counseling regarding prognosis. In all cases of Hunter syndrome caused by contiguous gene deletions or, the more, complex chromosomal rearrangements, other genetic factors likely contribute to the phenotype.

This is illustrated in Figs 3 and 4, where anthropometric data are presented. The most significant reductions of weight and height were noted in patients 1 and 2 (with deletions resulted from chromosomal aberrations; Fig. 4). The same parameters in patient 3 increased with age. Such a noticeable difference refers primarily to our probands' heights in Fig. 4, which steadily decreased in patients 1 and 2, while in patient 3 (nondeleted) increased (to 30 months).

Conclusion

We do not generalize with reference to other patients described in the literature but, based on two presented patients (1 and 2), we would like to emphasize that in the case of *IDS* gene deletion associated with complex chromosomal rearrangement, the MPSII phenotype may not be recognizable (or severe) itself, and neurodevelopmental disorders which likely are associated with other deleted/duplicated genes in the rearrangement dominate the patients' clinical picture. The prognosis is not straightforward and often difficult to predict. For genetic counseling, including recurrence risk, analysis of parental karyotypes is important.

Ethical approval and informed consent has/have been obtained and mentioned in the text.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

Bondeson ML, Dahl N, Malmgren H, Kleijer WJ, Tönnesen T, Carlberg BM, Pettersson U (1995). Inversion of the IDS gene resulting from recombination with IDS-related sequences is a common cause of the Hunter syndrome. *Hum Mol Genet* **4**:615–621.

Bondeson ML, Malmgren H, Dahl N, Carlberg BM, Pettersson U (1995). Presence of an IDS-related locus (IDS2) in Xq28 complicates the mutational analysis of Hunter syndrome. *Eur J Hum Genet* **3**:219–227.

Brusius-Facchin AC, De Souza CF, Schwartz IV, Riegel M, Melaragno MI, Correia P, *et al.* (2012). Severe phenotype in MPS II patients associated with a large deletion including contiguous genes. *Am J Med Genet A* **158A**:1055–1059.

Burton BK, Giugliani R (2012). Diagnosing Hunter syndrome in pediatric practice: practical considerations and common pitfalls. *Eur J Pediatr* **171**:631–639.

Froissart R, Da Silva IM, Maire I (2007). Mucopolysaccharidosis type II: an update on mutation spectrum. *Acta Paediatr* **96**:71–77.

Gort L, Chabás A, Coll MJ (1998). Hunter disease in the Spanish population: molecular analysis in 31 families. *J Inherit Metab Dis* **21**:655–661.

Hopwood JJ, Bunge S, Morris CP, Wilson PJ, Steglich C, Beck M, *et al*. (1993). Molecular basis of mucopolysaccharidosis type II: mutations in the iduronate-2-sulphatase gene. *Hum Mutat* **2**:435–442.

Kampmann C, Beck M, Morin I, Loehr JP (2011). Prevalence and characterization of cardiac involvement in Hunter syndrome. *J Pediatr* **159**:327–31.e2.

Neufeld EF, Muenzer J (2001). The metabolic and molecular bases of inherited disease. In: Scriver C, Beaudet AL, Valle D, Sly W, editors. New York: McGraw-Hill. p. 3421.

Scarpa M (2007). Mucopolysaccharidosis type II. [Updated 2018 Oct 4]. In: Adam MP, Ardinger HH, Pagon RA, *et al*, editors. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993–2019.

Vollebregt AAM, Hoogeveen-Westerveld M, Kroos MA, Oussoren E, Plug I, Ruijter GJ, *et al*. (2017). Genotype-phenotype relationship in mucopolysaccharidosis II: predictive power of IDS variants for the neuronopathic phenotype. *Dev Med Child Neurol* **59**:1063–1070.

Wraith JE, Scarpa M, Beck M, Bodamer OA, De Meirleir L, Guffon N, *et al*. (2008). Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. *Eur J Pediatr* **167**:267–277.

Zanetti A, Tomanin R, Rampazzo A, Rigon C, Gasparotto N, Cassina M, *et al*. (2014). A hunter patient with a severe phenotype reveals two large deletions and two duplications extending 1.2 Mb distally to IDS locus. *JIMD Rep* **17**:13–21.