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Case Report

Incidental diagnosis of mucopolysaccharidosis type I in an infant with chronic intestinal pseudoobstruction by exome sequencing

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ABSTRACT

Chronic intestinal pseudoobstruction (CIPO) is a severe form of intestinal dysmotility, and patients often undergo iterative abdominal surgeries and require parenteral nutrition. Several genes are known to be responsible for this pathology, including *ACTG2* (autosomal dominant) and *MYH11* (autosomal recessive).

We report the first case of unexpected trio medical exome sequencing diagnosis of mucopolysaccharidosis type I (MPS-I) in a patient with an early CIPO. There was no clinical suspicion of MPS-I at the time of the prescription. It allowed biochemical confirmation of MPS-I, expert clinical evaluation and early treatment. Enzyme replacement therapy (ERT) with laronidase was started at 9 months old, and hematopoietic stem cell transplantation was carried out at 10 months and a half. The patient also had a 1.7 mb heterozygous deletion in chromosomal region 16p13.11p12.3, comprising several genes, including *MYH11,* paternally inherited. Her father has no symptoms of CIPO or other digestive symptoms. One previous association of CIPO and MPS-I was reported in 1986. Moreover, the number of incidental findings of inherited metabolic disorders with therapeutic impact will inevitably increase as pangenomic analyses become cheaper and easily available.

1. Introduction

Chronic intestinal pseudoobstruction (CIPO) is a severe form of intestinal dysmotility characterized by the impairment of gastrointestinal propulsion of the gut content in the absence of occluding lesions. The disease is classified as primary if no demonstrable cause is detected, or secondary to many different diseases [1]. Affected patients may undergo iterative abdominal surgeries for resection of dilated bowel segments and enterostomies (gastrostomy, jejunostomy). Patients often require total or partial parenteral nutrition exposing to long term complications. The diagnostic workup aims to identify the causes, to understand the pathophysiologic features and to address the therapy, which requires a multidisciplinary approach. Milunsky et al. [2] found an *ACTG2* mutation in 49 out of 111 published probands with CIPO [44,1%] suggesting genetic heterogeneity. *ACTG2*-related disorder includes a spectrum of phenotypes: CIPO, megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) and Prune belly sequence.

Otherwise *MYH11* is one of the main differential diagnoses in the spectrum of CIPO and MMIHS. Compound heterozygous *MYH11* pathogenic variants were identified in a child with MMIHS and patent

Abbreviations: CIPO, Chronic intestinal pseudoobstruction; MPS-I, mucopolysaccharidosis type I; GAGs, glycosaminoglycans; ERT, enzyme replacement therapy; HSTC, hematopoietic stem cell transplantation; ACMG, American College of Medical Genetics and Genomics; ENT, Ear, Nose and Throat; IFs, Incidental findings; SFs, Secondary findings

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ductus arteriosus [3] and then, a new homozygous *MYH11* mutation was published in a neonatal patient with fixed dilated pupils and pulmonary, bladder, and bowel dysfunction [4].

We report the first case of incidental diagnosis of mucopolysaccharidosis type I in a patient for which genetic testing was performed because of an early CIPO diagnosis and discuss the therapeutic implications.

2. Case report

A genetic consultation took place for a 3-month-old infant during her hospitalization at the request of gastro-paediatricians because of an unusually early diagnosis of CIPO.

She was the second child of unrelated parents, born at 33 weeks' gestation by lower-segment caesarean section for cardiac rhythm abnormalities and decreased active fetal movements. No immediate perinatal problems were reported, APGAR score was 10 at 1 min and 3 min. At birth her weight was 2.3 kg (47th percentile), length 47 cm (75th percentile), head circumference 29.5 cm (5th percentile). From 3 weeks old she presented recurrent intestinal pseudo-occlusion leading to an early colostomy followed by an ileostomy and requiring total parenteral nutrition. Head circumference regularly followed the −2 standard deviations growth pattern and clinical examination was unremarkable except a doubtful axial tone (probably related to the context of hospitalization and the jugular catheter impeding movement). Genetic investigations by array-CGH and *ACTG2* sanger sequencing were performed after parental information and consent.

Array-CGH analysis revealed a 2.7 megabases heterozygous deletion in chromosomal region 16p13.11p12.3, comprising several genes, including *MYH11* (Myosin, heavy chain 11, smooth muscle) and published as causing microcephaly, variable developmental delay and behavioral abnormalities [5]. Fig. 1 shows the deletion in the software Decipher.

The familial segregation analyses showed that the deletion was inherited from her father. His head circumference was 54 cm (−1.5 SD), he studied until professional baccalaureate and did not present any digestive symptom.

As *MYH11*-sanger sequencing was not easily available in France and given that the described evolution was severe and quickly lethal in the two only patients reported in the literature at the time (3,4), a trio medical exome (which covers 5.500 OMIM genes and 11.884.205 base pairs) sequencing of the 5-month-old patient and her parents was performed. Methods are available in appendix.

The result was unexpected: no pathogenic variant in *MYH11* was found but the patient was compound heterozygous for two probably pathogenic mutations in *IDUA* (alpha L-iduronidase – OMIM #252800), the causal gene of mucopolysaccharidosis type 1 (MPS-I). Maternal mutation was c.1205G > A or p.(Trp402*), classified as pathogenic (ACMG class 5) [6]; and c.536C > T or p.(Thr179Met) classified likely pathogenic (ACMG class 4) was inherited from the father (genome reference hg19, NM_000203.3).

Therefore, the MPS-I incidentally diagnosed by medical exome sequencing was confirmed by the elevation of urinary glycosaminoglycans (GAG) at 39.9 mg/mmol of creatinine (normal 7.9 to 26.9), which contained high level of heparan and dermatan sulfate; and a very low activity of the lysosomal enzyme α-L-iduronidase: 2.88 µmol/h/mg of cellular protein for a normal between 12.2 and 41.8 µmol/h/mg of cellular protein and a technical witness activity of 40.7 µmol/h/mg of cellular protein (0.8 µkat/kg of cellular protein for a normal between 3.4 and 11.6 µkat/kg of cellular protein) verified in a second blood sample.

At seven and half months old, the patient's weight was 7.5 kg (−0.5 SD), length at 66 cm (mean) and head circumference at 39.7 cm (−2.5 SD). Clinical examination revealed an already known plagiocephaly, a round face with perhaps slightly coarse facial features, and nasal obstruction. There was no history of repetitive nasopharyngeal infection, no hernia. She was smiling and attentive. She could roll from back to tummy, sit propped up with hands, catch and move objects from one hand to the other. She babbled during the examination.

She had a clinical examination with a specialist of mucopolysaccharidoses at 8 months-old, who confirmed the diagnosis clinically: she had compatible facial features with thickened skin, slight stiffness of shoulder joints, no thoracolumbar kyphosis, no contractures, no hepatosplenomegaly, no hernia and presented a psychomotor delay.

Fig. 2 shows the progressive evolution of the patient's facial features at each genetic examination.

She underwent a basal assessment at diagnosis according to the method recommended by Clarke et al. in 2017 [7]:

- echocardiography and electrocardiogram were normal: no argument for valvular disease was found,
- abdominal ultrasound did not find hepatosplenomegaly,
- complete skeletal x-ray was normal: including no dysplastic vertebral body, no anterior beaking, skeletal age was estimated at 3-months-old (Greulich and Pyle method) for a real age of 8 months,
- ophthalmologic examination showed a normal cornea and funduscopic examination,
- cerebral and medullar MRI found no signal alteration, no enlarged periventricular spaces, no ventriculomegaly and no spinal stenosis, but a mild myelinization delay,
- pulmonary assessment found no frequent upper respiratory-tract infections, and no sleep apnea, but chronic rhinitis and ENT examination by nasofibroscopy noticed unclear mucoid secretions,
- auditory evoked potentials and audiometry were normal, no hearing

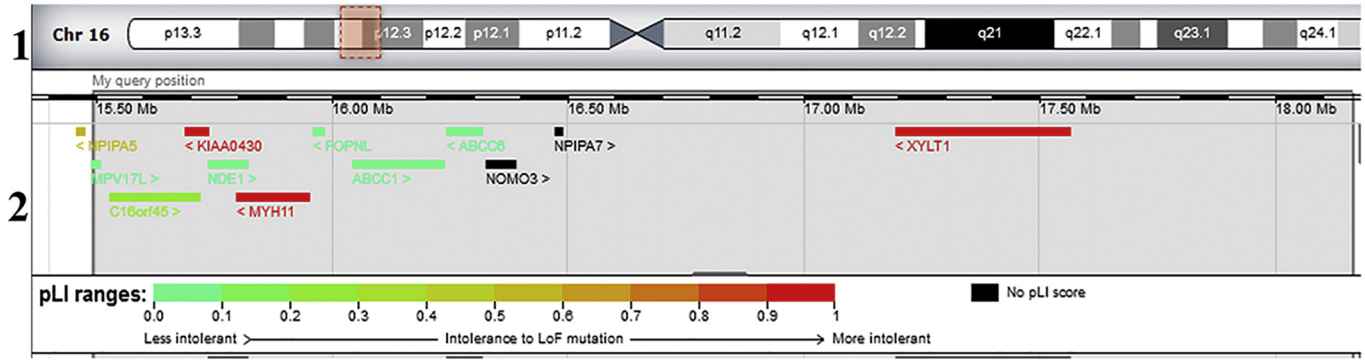

Fig. 1. Deletion of 2.7 megabases in the chromosomal region 16p13.11p12.3 found in array-CGH.
(1) the red dotted square shows the position on the chromosomal track.
(2) specifies OMIM genes included in the copy number variation (CNV). *MYH11* is included in the deletion with a hight pLi score, indicating a low tolerance to variation.

Fig. 2. patient evolution at different genetic examinations.

loss was found.

After confirmation of diagnosis, enzyme replacement therapy (ERT) with laronidase was started at 9 months old. [8,9]. She had a neuropsychologist evaluation at this age, which found a heterogeneous profile development depending on competences domains on the Brunet-Lézine revised scale. About the gross motor skill, she presented acquisitions of a 5 months old infant (developmental quotient for posture DQP: 64). She could hold up the head securely and started to sit independently when placed in a sitting position. She could roll back to front. Fine motor skill development corresponded to a 6 months old infant (quotient for hand-eye coordination DQC: 81). She reached and grasped a toy and transferred an object from hand to hand but she did not use her thumb and forefinger to grasp. Language performances were equivalent to a 5 and half-months old infant (developmental quotient for language DQL: 70). She babbled but did not play peek-a-boo.

Socialization abilities were similar to a 6 months old infant (developmental quotient for socialization DQS: 77). She was interested in her environment and recognized familiar people. Global development age was 5 and half-months at 9 months old.

The French Committee for the Evaluation of the Treatment of Lysosomal Diseases (CETL: http://www.cetl.net/) recommended hematopoietic stem cell transplantation (HSCT) and ERT to be continued six months after HSCT, in this context of early diagnosis of an attenuated type I mucopolysaccharidosis (Hurler-Scheie) [10].

A myeloablative HSCT was carried out at 10 and half-months old for this patient, with a matched unrelated donor in absence of matched sibling donor.

Three months after transplantation activity of the lysosomal enzyme α-L-iduronidase was 12.4 μkat/kg of cellular protein (normal 3.4 to 11.6), and there were no dermatan and heparan sulfate in urine. She was treated by Ruxolitinib and corticoid for a grade 2 cutaneous graft *versus* host disease.

Twelve months after HSCT, activity of the lysosomal enzyme α-L-iduronidase was 25.56 μmol/h/mg of cellular protein for a normal between 12.2 and 41.8 μmol/h/mg of cellular protein and a technical witness activity of 40.7 μmol/h/mg of cellular protein (7.1 μkat/kg of cellular protein for a normal from 3.4 to 11.6 μkat/kg of cellular protein), there were traces of dermatan and heparan sulfate in urine. Post-transplantation chimaerism study in peripheral blood showed a nearly full donor predominance with recipient fraction at 0.65%.

At the last clinical examination, she was 27 months old. She developed an HSCT autoimmune complication which required steroids, rituximab and cyclophosphamide injections to treat the haemolytic anaemia.

She had walked at 24 months old. Language began to settle with new vocabulary each day but no association of two words. On Denver scale socialization was at 22 months old, language was at 21 months old, gross and fine motor were at 24 months old. There was no thoracolumbar kyphosis, but slight stiffness of shoulder joints, no contractures. Cardiopulmonary examination was normal. She still had parenteral nutrition to supplement the diet because of the CIPO.

3. Discussion

We report here an unexpected medical exome diagnosis of MPS-I in a pauci-symptomatic 8-month-old infant. To our knowledge this is the second report of the association of CIPO and MPS-I. One previous association of CIPO and MPS-I was reported in 1986 in a japanese journal, the title mentions an attenuated MPS-I (Scheie disease). Unfortunately, this publication in japanese is not available [11].

Pangenomic analysis such as array-CGH or exome sequencing can lead to the finding of a variant that is associated with a condition other than the one for which testing was originally indicated. In clinical exome sequencing, incidental findings (IFs) are unintentionally revealed variants and secondary findings (SFs) are actively pursued but unrelated with the supposed diagnosis variants. IFs and SFs are the subject of various reporting guidelines and policy documents based on ethical arguments, concerning autonomy, non-maleficence and beneficence [12,13]. Reported percentages of SFs in exome sequencing studies was nearly 1% in cancer susceptibility genes [14], from 1.2% to 3.4% for 114 genes in a 1.000 exomes sequencing study [15] and 8.8% in 159 families participating in the NIH Undiagnosed Diseases Program [16]. The American College of Medical Genetics and Genomics (ACMG) proposed a list of 59 genes for which secondary findings should be reported. Those were chosen because they are associated with conditions that have a definable set of clinical features, the possibility of early diagnosis, a reliable clinical genetic test, and effective intervention or treatment. *IDUA* variants are not in this list despite the fact that an active treatment exists.

In 2019 Belgian centres for medical genetics [17] were asked about their practice for reporting criteria for IFs disclosure, which was determined by an interaction between the clinical significance and patient-related factors. International guidelines for the reporting of IFs might be effective only when they are sufficiently detailed but allow reflection for each individual case [17].

For this patient, the genetic and biochemical confirmation of MPS-I was possible before any of the usual specific disease early signs such as thoracolumbar kyphosis with dysplastic vertebral body, hepatosplenomegaly or typical coarse features. She had a global development delay, which could have been attributed to her prolonged hospitalizations since the neonatal period. The coincidence of two rare chronic diseases is uncommon in pediatric patients, and unusual symptoms in the context of CIPO may have been overlooked.

This diagnosis led to an early treatment with laronidase ERT and hematopoietic stem cell transplantation. The activity of the lysosomal enzyme α-L-iduronidase was normalized at twelve months after the HSCT. To our knowledge, laronidase ERT digestive efficacity have not been studied yet. Meta-analysis by Dornelles et al. [18] reported that laronidase effectively reduces urinary GAGs excretion, hepatomegaly and left ventricular mass index and can improve shoulder flexion in MPS-I patients.

This early management with HSCT at 10 and half months allows a more optimistic psychomotor and neurological development than usually observed. Long-term efficacity of HSCT and ERT (14 years follow-up) in Hurler syndrome have been studied by Eisengart et al. [19]. This study showed the superiority of HSCT in survival and a clear reduction risk of hydrocephalus and cervical cord compression.

A prospective follow-up will be necessary to evaluate if the early treatment is developmentally beneficial and prevent the occurrence of complications, particularly neurological, digestive, respiratory and ENT.

Moreover, *MYH11* autosomal recessive loss-of-function mutations lead to MMIHS. Clinical features include bowel and bladder obstructions [20]. Most common symptoms are abdominal distension, absent or decreased bowel sounds, failure to pass meconium and inability to avoid requiring catheterization. Patients undergo surgical interventions such as enterostomies (gastrostomy, jejunostomy) for nutrition administration and bowel decompression, and total parenteral nutrition can be required due to intestinal failure from intestinal dysmotility [21–23]. Furthermore, recent studies incriminated dominant *MYH11* causal variants in CIPO [24] and in severe gastrointestinal dysmotility [25]. To our knowledge, no deletion in chromosomal region 16p including *MYH11* and causing a phenotype of CIPO have been described before.

Therefore, *MYH11 (*Myosin, heavy chain 11, smooth muscle) haploinsufficiency associated with the two *IDUA* pathogenic mutations might induce a cumulative effect explaining digestive disorders in foreground in this patient.

Missense mutations in *IDUA* are typically associated with attenuated MPS-I, on the contrary nonsense mutations are typically implicated in a severe phenotype. Compound heterozygotes for a nonsense mutation and a missense mutation have a wide range of clinical phenotypes, depending on the severity of the missense mutation. For this patient who presents a nonsense and a missense mutation, this second variation may have a moderate severity [26,27].

In conclusion, in our case informing the family from the MPS-I incidental genetic diagnosis was critical to introduce early specific treatments, and may improve the neurodevelopmental prognosis. Pangenomic analyses will inevitably lead to an increase in the number of incidental findings of inherited metabolic disorders in the coming years.

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Appendix A

A.1. Array-CGH

Oligonucleotide array-CGH was performed using the Agilent Human Genome CGH microarray 4x180K (Agilent Technologies, Santa Clara, CA, USA). The experiment was performed according to version 7.5 (June 2016) of the protocol provided by Agilent (Agilent Oligonucleotide Array-Based CGH for Genomic DNA Analysis).

A.2. Exome sequencing

A.2.1. Sequencing technologies

All samples were prepared with the Agilent Focused Exome preparation kit (which covers 5500 genes associated with known phenotypes and 11,884,205 base pairs) and sequenced on an Illumina NextSeq 5500 sequencer using 2 × 75 bp sequencing kits. Briefly, gDNA is first fragmented by enzymatic protocol and DNA ends are modified with adaptor-tag for target enrichment. After amplification and purification, adaptor-ligated libraries are hybridized to SureSelect Focused Exome and captured prior to indexing. Samples are then pooled for multiplexed sequencing.

A.2.2. Bioinformatics pipeline

Raw sequencing data were mapped to the GRCh37/hg19 reference genome with the bwa-mem aligner (Li et al. 2009). The identification of variants have been performed using Freebayes and the GATK (Unified Genotyper and Haplotype Caller) (Van der Auwera 2013). When possible, the calling has been conducted in a family structure.

Variants were annotated using ANNOVAR (Wang *et al*, 2010, build of February 2016) based on RefSeq genes, known variation from dbSNP144, and Clinvar and frequencies from 1000 Genomes Project, esp6500 project, Exac (Lek et al. 2016) and kaviar (Glusman et al. 2011) database.

The functional consequence of missense coding variants has been assessed using dbNSFP v.3.0 (Liu *et al*, 2015) that includes several deleteriousness prediction algorithms (SIFT, PolyPhen2 HDIV, PolyPhen2 HVAR, LRT, MutationTaster, MutationAssessor, FATHMM, MetaSVM, MetaLR, VEST, CADD, GERP + +, DANN and PROVEAN). In order to facilitate the interpretation of these results, a summarizing value reflecting the percentage of predictions that classify this variant as deleterious has been calculated. For splices site prediction annotations we used SpliceSiteFinder-like, MaxEntScan, NNSPLICE and GeneSplicer.

The variants were further prioritized based on the variant type, the deleteriousness predictions, OMIM and ClinVar informations and the potential candidate genes list.

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