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Case Report

Neonatal heart failure and noncompaction/dilated cardiomyopathy from mucopolysaccharidosis. First description in literature

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ABSTRACT

Mucopolysaccharidosis are genetic disorders due to deficiency of lysosomal enzymes, resulting in abnormal glycosaminoglycans accumulation in several tissues. Heart involvement tends to be progressive and worsens with age. We describe the first case of mucopolysaccharidosis type I presenting with noncompaction/dilated-mixed cardiomyopathy and heart failure within neonatal period, which responded successfully to specific metabolic treatment. Cardiac function recovered after enzyme replacement therapy and hematopoietic stem cell transplantation, adding to the existing knowledge of the disease.

1. Case description

A 13-days neonate, born from consanguineous African parents, was referred to local hospital for respiratory distress and feeding difficulties. On chest radiographs, cardiomediastinal silhouette was slightly enlarged, but no pulmonary consolidations nor pleural effusion were detected. Electrocardiogram was unremarkable, but on echocardiogram hypokinetic cardiomyopathy with mild left ventricular (LV) dysfunction was noted. Given the evidence of cardiomyopathy, a complete metabolic workup was performed, comprehensive of quantitative measurement of aminoacids in plasma and urine, plasma acylcarnitines analysis, urine organic acids and glycosaminoglycans (GAGs) analysis. Unexpectedly, urine analysis showed elevated GAGs levels. Thus, at the age of six weeks baby was referred to our hospital for metabolic evaluation.

On admission, the patient was afebrile and in discrete clinical conditions. Clinical examination documented tachypnoea (respiratory rate 50/min) with use of accessory muscles, tachycardia (heart rate 174 bpm), hepatomegaly and prolonged refill time (3 s). Blood pressure and oxygen saturation were normal. Mild facial and somatic dysmorphisms were noted: enlarged lips, gingival enlargement, third right nipple, diastasis recti with umbilical hernia. Extraocular movements were intact and eye contact sporadic. Reflexes were symmetric, including Moro reflex. Cardiac auscultation revealed protodiastolic gallop rhythm (S1, S2, S3), without murmur, rub nor thrill; peripheral pulses were symmetric. Lungs were clear to auscultation bilaterally, without crackles or wheezes. No skeletal deformities were present, but we appreciated a limitation at hips abduction. No oedema, cyanosis nor clubbing could be noticed. Echocardiogram confirmed mixed noncompaction/dilated cardiomyopathy (Fig. 1) with mild LV dysfunction: LV end-diastolic diameter was 26 mm (*Z*-score 3.3), LV end-systolic diameter 17 mm (Z-score 2.8), LV ejection fraction (LVEF) 50% (see Supplementary data online, Video 1). Mild mitral valve regurgitation was also detected (see Supplementary data online, Video 2), whereas coronary artery anomalies were excluded.

Urine analysis confirmed elevated GAGs levels (2373.60 mg/g creatinine, normal value <290); qualitative test showed a dermatan

Abbreviations: ERT, Enzyme Replacement Therapy; GAGs, Glycosaminoglycans; HSCT, Hematopoietic Stem Cell Transplantation; LV, Left Ventricular; LVEV, Left Ventricular Ejection Fraction; MPS, Mucopolysaccharidosis.

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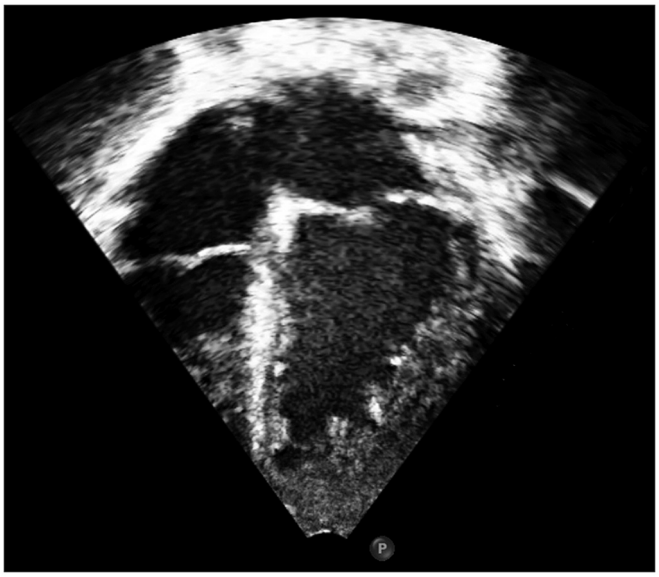

Fig. 1. Apical four chamber echocardiogram view on admission Left ventricle appears mildly dilated, with noncompaction aspect of its apex and parietal wall.

sulfate spot. Alpha-L-iduronidase activity measured by tandem mass spectrometry was deficient in dried blood spot (1.3 umol/l/h, normal value >1.58; control enzyme: alpha-glucosidase) and undetectable in leucocytes (0.1 nmol/mg/h, normal value 25–60), consistent with the suspicion of mucopolysaccharidosis (MPS) I. Diagnosis was confirmed by genetic testing as patient proved homozygous for the mutation c.46_587del12 in alpha-L-iduronidase gene, associated with Hurler phenotype [1].

Medical treatment for hearth failure was started (bisoprolol 0.2 mg/kg PO q12hr, captopril 0.5 mg/kg PO q12hr) with transient improvement in clinical conditions and initial stabilization of ventricular function. Two weeks later, child's clinical conditions worsened with exacerbation of congestive heart failure (dyspnoea, tachycardia, hepatomegaly, gallop rhythm). A further reduction in LV systolic function (LVEF 35–40%) was documented, along with moderate mitral regurgitation. Intravenous diuretic treatment was started (furosemide 1 mg/kg IV q12hr), while cardioactive treatment with ACE inhibitors and beta-blockers was progressively increased according to clinical status and patient tolerance (bisoprolol 0.2 mg/kg PO q12hr, captopril 0.8 mg/kg PO q8hr). At the age of two months, enzyme replacement therapy (ERT) for MPS I was started (laronidase at standard dosage 100 UI/kg weekly): rate and volume of infusions were standard (50 ml in 4 h) with no restrictions for heart failure and no adverse events were documented. In the following weeks, progressive improvement in clinical conditions and systolic function (LVEF 55%) were achieved. Two months later, given the stability of her clinical conditions, the child underwent allogeneic hematopoietic stem cell transplantation (HSCT) from haploidentical donor (sister) who was non-carrier for the alpha-L-iduronidase gene mutation. Conditioning regimen for HSCT included busulfan (4 mg/kg IV qDay) and fludarabine (40 mg/mq IV qDay). Immunosuppressant therapy included cyclosporine (3 mg/mq/qDay OS) and methotrexate (10 mg/mq qDay IV). ERT was continued for a period of three months after HSCT.

Acute worsening in clinical status with transient haemodynamic decompensation was documented in the early post-transplant period, with reduction in cardiac function on echocardiography. The child required inotropic treatment and intravenous diuretics for 7 days (milrinone IV 0.6 μg/kg/h and furosemide 0.2 mg/kg/h IV) until stable haemodynamic balance was achieved. In the following days, patient's clinical conditions gradually improved and progressive switch to oral treatment was performed (furosemide 1 mg/kg OS q12hr then tapered to 0.3 mg/kg q12hr, carvedilol 0.5 mg/kg PO q12hr, captopril 0.8 mg/kg PO q12hr). At the age of 18 months, complete recovery in LV systolic function and resolution of mitral regurgitation were documented on echocardiographic follow-up (see Supplementary data online, Videos 3 and 4); however, LV noncompaction was still evident. Given the persistent recovery of normal left ventricular function, cardioactive treatment was gradually reduced and then stopped at 2 years of age. Finally, as far as neurocognitive function is concerned, the child showed minor developmental delay: she walked by 18 months and by 2 years of age she had reached basic language comprehension and production (she could point to things or pictures when they were named and knew names of familiar people).

2. Discussion

MPS comprises a group of genetic disorders characterized by a deficiency of the lysosomal enzymes involved in the degradation of GAGs. Impaired enzymatic activity results in abnormal GAGs accumulation in several tissues, leading to progressive involvement of multiple organs as skin, bone, joints, and eye up to nervous system. Heart involvement due to intracardiac infiltration of GAGs is a common feature in MPS I, reported in up to 80% of patients. Cardiac storage of GAGs involves valves, conduction system, coronary arteries and myocardium, leading to valvular disease, arrhythmia, coronary artery disease and cardiomyopathy. The most prominent cardiac manifestation in MPS I is valvular abnormality [2], followed by hypertrophy: in MPS I 50% of patients have increased left ventricular mass due to concentric hypertrophy [3]. To our knowledge, this is the first report documenting mixed noncompaction/dilated cardiomyopathy in MPS. Since mixed noncompaction/dilated cardiomyopathy has never been described in MPS I, it could be argued that this may be due to another underlying genetic or metabolic abnormality. Interestingly, left ventricular noncompaction has been described as associated with other inborn errors in metabolism, as Barth syndrome and further mitochondrial disorders [4–6]. However, excluding the elevated GAGs levels in urine analysis, the complete metabolic workup in our patient proved to be normal. More importantly, the cardiomyopathy responded successfully to specific metabolic treatment for MPS I, including ERT and HSCT. This is why we believe that the cardiomyopathy in our patient was reasonably related to MPS I.

Secondly, despite cardiac involvement in MPS may be very early, the disease is commonly silent during the first months of life: cardiovascular symptoms tend to appear later and worsen with age [7,8]. Few reports have described cardiac failure as a presenting feature of MPS I in infancy, at a time when the other signs of the condition may be subtle or nonspecific [9–11]. We report the first description of mixed noncompaction/dilated cardiomyopathy due to MPS I presenting with heart failure within neonatal period.

Notably, cardiomyopathy in MPS I can occur early in life [2] and early-onset cardiac disease is commonly associated with the rapidly progressing form of MPS I [12]. Even though clinical signs and symptoms of cardiac involvement are uncommon, leading to an underestimate of the true prevalence of cardiac disease, up to half of all patients with severe MPS I die from cardiac causes, congestive heart failure or sudden arrhythmia [2]. So far, early recognition of MPS I is mandatory in order to perform a complete cardiac evaluation in affected patients, and then start prompt metabolic and cardioactive treatment. In fact, systemic therapies as HSCT or HSCT combined with ERT have shown to lengthen life, to improve clinical status, particularly when performed early in life, and to arrest neurological deterioration in the rapidly progressing form of MPS I [12]. HSCT and ERT proved also to preserve cardiac function and improve cardiac hypertrophy in patients with MPS [2,13]. Our experience is consistent with these findings, since stable recovery in cardiac function was documented after 12 months from treatment (HSCT and ERT). Thus, our experience highlights an

important message: given the availability of effective treatment options, complete metabolic screening, including tests for MPS, must be considered in all neonates and infants presenting with inexplicable heart failure and cardiomyopathy, including not only hypertrophic cardiomyopathy but also mixed and noncompaction phenotypes. We confirm also that when heart failure is present in MPS I, ERT pre-transplant can improve cardiac function sufficiently to permit safe HSCT using myeloablative conditioning [14]: our patient achieved a normal cardiac function on proceeding to transplant and tolerated the standard conditioning regimen which included cardiotoxic chemotherapeutic agents as busulfan. In fact, the child, despite developing a transient cardiorespiratory deterioration in the early post-transplant period, responded successfully to inotropic support and diuretic treatment, achieving complete recovery in cardiac function.

Finally, from 2018 MPS I has been included among the conditions identifiable through the *Expanded Newborn Screening*, which is currently mandatory for all the neonates born in Tuscany. The reported child did not undergo this expanded screening: in fact, the diagnosis of lysosomal disorder was precocious but quite unexpected and achieved only after the child developed severe clinical manifestations. The availability of effective treatment for MPS I underlines the importance of a broader application of the *Expanded Newborn Screening*, in order to detect the disease as early as possible for a better outcome.

3. Disclosure of potential conflicts of interest

Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100714.

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