Case Report

Long-term follow-up of metachronous marrow-kidney transplantation in severe type II sialidosis: what does success mean?

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Introduction

Sialidosis is a rare lysosomal storage disorder, characterized by deficient lysosomal neuraminidase (NEU1) activity and aberrant accumulation of sialylated glycoconjugates [1]. Affected sialidosis patients are divided into two groups [1,2]. Type I (normomorphic) sialidosis, an attenuated non-neuropathic form of the disease, is associated with cherry-red spot myoclonus syndrome, occurring in the second decade of life, and progressively impaired vision. Type II (dysmorphic) sialidosis, the severe, neuropathic form, comprises two subtypes based on the age of onset and the clinical severity: early infantile severe type—with a possible congenital or antenatal (hydropic form) onset—and late infantile or juvenile (onset after 1 year of age) type. All patients with type II sialidosis eventually demonstrate a progressive mucopolysaccharidosis (MPS)-like phenotype, including cherry-red spot myoclonus, coarse facies, visceromegaly, dysostosis multiplex, and severe mental retardation due to rapidly progressive encephalopathy [1–3]. Patients with congenital type II sialidosis present with hydrops foetalis, neonatal ascites, or both; these patients are either stillborn or die shortly after birth [1]. Within the first years of life, a few type II sialidosis patients develop a nephropathy related to kidney storage. Such a phenotype was named ‘nephrosialidosis’.

To date, treatment options for sialidosis remain limited and are directed primarily at supportive care and symptomatic relief. Bone marrow transplantation (BMT) has been widely used with success in Hurler’s disease [3] before onset of severe neurological impairment, but no sialidosis patient treated by BMT has ever been published. We report the clinical outcome and long-term follow-up of a unique sialidosis type II patient who underwent metachronous marrow-kidney transplantation. We also compare this patient with the other nephrosialidosis patients reported in the literature and propose several hypotheses in order to explain BMT inefficiency in preventing renal involvement.

Case report

The patient was the first child of non-consanguineous parents. Pregnancy was uneventful but hydramnios was noted. At birth, this female newborn suffered from oedema and was admitted at 1.5 months of age because of failure to thrive and vomiting. On admission, she presented with limb oedema, liver and spleen enlargement together with dysmorphic features (coarse facial features, depressed nasal bridge and gingival hyperplasia). A slight axial hypotonia and poor ocular contact were mentioned. Bone X-ray was consistent with dysostosis multiplex. These findings suggested a diagnosis of either mucopolysaccharidosis or oligosaccharidosis. Urinary mucopolysaccharide profile was normal but oligosaccharide profile was compatible with sialidosis. This diagnosis was confirmed by a complete deficiency of α-D-neuraminidase activity with normal β-galactosidase activity in cultured skin fibroblasts. In the absence of advanced neurological impairment, an allogenic BMT was performed at 9 months of age; engraftment was successful without relevant complications.

Asymptomatic isolated proteinuria was noted at 25 months of age, reaching 0.8 g/24 h at 3 years of age. A renal biopsy was therefore performed and showed glomerular epithelial and tubular cells enlargement due to large cytoplasmic vacuolization (Figure 1).
Renal failure further progressed (SCr = 170 μmol/l at 5 years of age) so that haemodialysis was required at age 6. A cadaver kidney Tx was performed 1 year later with uneventful post-operative period (normal GFR, no proteinuria).

However, at 11 years of age, the general condition of the patient remained rather poor. She presented with psychomotor retardation (non-verbal development quotient = 51) and significant disabling due to severe musculoskeletal involvement, mainly kyphoscoliosis. She has developed profound anorexia with subsequent malnutrition (body weight = 16 kg, −3.5 SD; length = 97 cm, −6 SD; Body Mass Index = 17) and was tremendously psychologically affected.

**Discussion**

BMT did not prevent bone involvement; this was predictable when referring to Hurler’s disease in which over 300 cases of BMT have been reported [4]. The rapidly progressive and severe encephalopathy usually associated with type II sialidosis was indeed prevented, but our patient presented with an obvious psychomotor delay (without regression), which should be regarded as an attenuated feature of neurological involvement. In addition, renal manifestations in relation to kidney storage were not prevented by BMT since the patient had no renal impairment prior to BMT, but further progressed towards end-stage renal failure.

Several hypotheses can be proposed to explain such an unexpected result: (i) donor cells (i.e. lymphocytes and monocytes) might be poorly targeted to kidney tissue, (ii) the neuraminidase requirement of kidney may be important regarding the high content of this tissue in sialyloligosaccharide compounds, and (iii) renal cell turnover is rather slow and that may lead to dramatic sialyloligosaccharide lysosomal storage. The inability of BMT to prevent renal storage in another lysosomal storage disease, i.e. Fabry’s disease, has been demonstrated in knock-out mice, which are unable to show any reversal of substrate accumulation [5].

Maroteaux et al. [6] first reported sialidosis with overt renal involvement and named this ‘new type of sialidosis’, ‘nephrosialidosis’ [6,7]. Further case reports [8–10] included patients with early forms of severe type II sialidosis who had progressive proteinuria leading to uraemia; all of them presented renal pathological features identical to those found in our patient. We therefore suggest that nephrosialidosis would be considered as a phenotype variant of type II sialidosis instead of a novel entity. However, there is no current explanation of the clinical expression of kidney disease in a limited number of patients who experience the same ubiquitous enzyme deficiency as patients who are free from renal manifestations. A longer patient life span may bring information. Differences in the genetic background should be taken into account as it can influence (i) tissue expression of the multienzymic complex (neuraminidase/β-galactosidase/protective protein) in which neuraminidase is included, (ii) the rapidity of sialyloligosaccharide metabolism, and (iii) many other metabolic pathways. In addition, several epigenetic factors may also play a role.

This is the first report of early infantile sialidosis treated with metachronous marrow-kidney transplantation. The rationale for BMT at 9 months of age was supported by the very favourable neurological outcome of children with Hurler’s disease who underwent BMT before 2 years of age [4]. One could expect a similar benefit in sialidosis. However, despite a good long term graft and patient survival, the overall result is rather poor in terms of quality of life, medical dependency and social rehabilitation. Such outcome raises major ethical issues, as even an earlier timing for BMT may not have prevented the need for a renal transplantation.

To date, therapeutic options for sialidosis are therefore very limited. BMT does not seem to be recommended in severe type II sialidosis patients as it is not able to prevent nephropathy nor psychomotor retardation, however, a recent report describes the use of enzyme replacement therapy (ERT) in a mouse model of early infantile sialidosis [11]. Mannosylated neuraminidase was produced in insect cells and infused alone or co-administrated with the stabilizing protective protein/cathepsin A produced in the same insect cells. These mannosylated proteins can reach reticuloendothelial cells of many tissues using the mannose receptors of these cells, but cannot cross the blood–brain barrier. Their infusion restored neuraminidase activity and decreased lysosomal storage in many tissues except brain and ear. However, ERT mice developed a severe immune response towards the exogenous neuraminidase. Such a severe immune response has been encountered in MPSI dogs but was overcome by immune suppressive therapy [12]. These data offer a real hope in the treatment of non-CNS sialidosis symptoms, especially kidney impairment.

The use of combine ERT and BMT could be one potential future option for treating type II sialidosis patients.

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References


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