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Abnormalities of acid–base balance and predisposition to metabolic acidosis in Metachromatic Leukodystrophy patients

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ABSTRACT

Metachromatic Leukodystrophy (MLD; MIM# 250100) is a rare inherited lysosomal storage disorder caused by the deficiency of Arylsulfatase A (ARSA). The enzymatic defect results in the accumulation of the ARSA substrate that is particularly relevant in myelin forming cells and leads to progressive dysmyelination and dysfunction of the central and peripheral nervous system. Sulfatide accumulation has also been reported in various visceral organs, although little is known about the potential clinical consequences of such accumulation. Different forms of MLD-associated gallbladder disease have been described, and there is one reported case of an MLD patient presenting with functional consequences of sulfatide accumulation in the kidney.

Here we describe a wide cohort of MLD patients in whom a tendency to sub-clinical metabolic acidosis was observed. Furthermore in some of them we report episodes of metabolic acidosis of different grades of severity developed in acute clinical conditions of various origin. Importantly, we finally show how a careful acid–base balance monitoring and prompt correction of imbalances might prevent severe consequences of acidosis.

1. Introduction

Metachromatic Leukodystrophy (MLD; MIM# 250100) is a rare inherited lysosomal storage disorder caused by the deficiency of Arylsulfatase A (ARSA). The enzymatic defect results in the accumulation of the ARSA substrate galactosylceramide I3-sulfate, also known as sulfatide, in the lysosomes of all cell types. Substrate storage is particularly relevant in myelin forming cells, both oligodendrocytes and Schwann cells, leading to progressive dysmyelination and dysfunction of the central (CNS) and peripheral (PNS) nervous system, respectively [1]. However, sulfatide accumulation has also been reported in various visceral organs (liver, gallbladder, kidney, pancreas, lymph nodes, adrenal glands, and ovaries) of post-mortem MLD patients [2,3], even though little is known on the potential clinical consequences of such accumulation. Some clinical reports describe MLD-associated gallbladder disease in different forms such as thickening of the gallbladder wall, gallstones, and polyposis [4–8], however, in only one case has an MLD patient been reported as presenting a functional consequence (moderate and persistent metabolic acidosis due to proximal tubular dysfunction) of sulfatide accumulation in the kidney [9].

Here we describe MLD patients who display sub-clinical metabolic acidosis at baseline and eventually develop overt metabolic acidosis of different grades of severity in acute clinical conditions, and show how a careful acid–base balance monitoring and correction of imbalances might prevent severe consequences of acidosis.

2. Patients and methods

The cohort of subjects here described is composed of 24 patients affected by late infantile (LI) (13/24) or early juvenile (EJ) (11/24) MLD, followed at our Institute within a natural history study [10] and more recently in the context of a phase I/II clinical trial of autologous haematopoietic stem cell gene therapy [11]; both clinical protocols

Abbreviations: ARSA, Arylsulfatase A; CNS, central nervous system; EJ, early juvenile; LI, late infantile; MLD, Metachromatic Leukodystrophy; PNS, peripheral nervous system; Pts, patients.

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were approved by the medical Ethic Committee of the San Raffaele Hospital in Milan. Fifteen patients are of Caucasian ethnicity (4 Italians, 4 Americans, 2 British, 2 Swedish, 1 Norwegian, 1 Polish, 1 Czech), 6 are Arab, 2 are of Hispanic origin (Brazilian), and one patient is of Turkish origin. The age range at observation is between 8 months and 18 years old.

All of the patients were retrospectively evaluated for acid–base balance in different phases of their disease, either very advanced in the case of the natural history study or before/in the early phases after symptom onset in the case of their enrolment in the gene therapy clinical trial. Furthermore, the patients enrolled in the gene therapy clinical trial were prospectively monitored for acid–base balance at +7 days and +3 months after gene therapy. Analyses performed on blood samples include acid–base balance parameters (pH, base excess, bicarbonates), serum electrolytes (sodium, chloride, potassium), creatinine, creatinine clearance (calculated with the Schwartz formula, mL/min per 1.73 m^2), and lactate; on urine samples pH, sodium, chloride, potassium and chemistry were evaluated. For patient #1 renin, aldosterone, dosage of essential amino acids in blood and urine, thyroid function and dosage of vitamin B1 were tested in the acute phase. For all these tests reference values of our internal laboratory (LaboRaf, San Raffaele Hospital, Milan, Italy) were used.

3. Results

Over the past 10 years, we have followed patients affected by MLD within a natural history study [10] and more recently in the context of a phase I/II clinical trial of autologous haematopoietic stem cell gene therapy [11]. In some of these patients, as part of their routine clinical management, acid–base balance was monitored by venous (pH, base excess, bicarbonate levels) and urinary (pH) assessments. In the context of the same routine management, serum electrolytes (Na, K, Mg, Ca, Cl) and creatinine clearance were repeatedly assessed in some of the patients. A total of 24 patients affected by late infantile (LI) or early juvenile (EJ) MLD were tested in different phases of their disease, either very advanced in the case of the natural history study or before/in the early phases after symptom onset in the case of their enrolment in the gene therapy clinical trial. For some of the patients repeated measurements were also collected during their follow-up, i.e. when they experienced acute clinical conditions.

3.1. Acid–base balance and acidosis in MLD patients in acute conditions

During their clinical course and follow-up, seven of the 24 patients (29%) developed a clinically-relevant metabolic acidosis, requiring supplementation of bicarbonates for either clinical management of acute clinical signs and symptoms, or in a preventive fashion based on laboratory venous acid–base findings. In all of the cases acidosis was documented in close association to an acute and stressful clinical event (Table 1). Also in the case of the patients enrolled and treated in the gene therapy clinical trial (Pts 1–6), acidosis occurred in occasion of acute events, such as main surgery or sepsis, either before or shortly after the administration of the chemotherapy regimen and of the autologous gene-modified cells envisaged by the gene therapy treatment (Table 1). In particular, treatment consisted of transplantation of autologous gene-modified haematopoietic stem cells after the administration of a myeloablative, dose-adjusted, intravenous (iv) busulfan chemotherapy. During the neutropenic phase, transplanted patients received prophylaxis for bacterial (Amoxocilin-clavulanic acid 50 mg/kg/day), viral (Acyclovir 15 mg/kg/day), *Pneumocystis jirovecii* (Pentamidin aerosol 9 mg/kg every 3 weeks) and fungal (liposomal B Amphotericin 1 mg/kg/day iv) infections.

Patient # 1 experienced two events of acute acidosis during severe episodes of febrile neutropenia and sepsis (day +11 and +37 post-transplant). High lactate levels in association with acidosis (pH 6.9%; bicarbonate 6 mmol/l, base-excess −28.8 mmol/L, pCO2 15.8 mm Hg, Lactate 14 mmol/L at first episode; pH 7.24%, bicarbonates 12.8 mmol/L, base-excess −13.3 mmol/L, pCO2 30.2 mm Hg and lactate 12.53 mmol/L at second episode) were detected in venous blood (Fig. 1). Urinary testing showed loss of glucose in urine in the presence of a normal serum glucose level. The first episode promptly resolved upon administration of bicarbonates and dedicated support measures (cristalloids, blood products, diuretics). Thereafter, she maintained a good acid–base balance without the need for bicarbonate supplementation until the second episode of sepsis and acidosis when iv bicarbonates were again employed for acute episode management. Upon resolution of the clinical event, bicarbonate supplementation was progressively decreased and completely stopped 18 months after transplant. Alkalinisation of urine (up to pH values of 8.5%) upon bicarbonate supplementation was documented. Of note, at a retrospective evaluation of patient's serum and urinary acid–base balance (2 months before treatment), we noticed pre-existing urinary borderline pH (equal to 7%) and elevated sodium renal excretion, suggesting that urinary loss of bicarbonates could have been already present in baseline conditions and that possibly it could not have been compensated for a stress situation. These findings associated with elevated sodium excretion, and in the absence of any other organic abnormality, were considered suggestive of a type II tubulopathy affecting the proximal tubule with decreased resorption of bicarbonates. To investigate whether another underlying cause of lactic acidosis was present and to understand the tubular defect in more detail, measurement of the levels of essential amino acids in blood and urine was performed, showing normal levels of amino acid in blood and increased level of urinary amino acids, compatible with type II tubulopathy. All the other kidney laboratory parameters including creatinine clearance were within normal limits. Renin, aldosterone, potassium, calcium, proteins and the calcium/creatinine ratio in urine were within normal limits. Thyroid function and level of vitamin B1 were normal. We thus confirmed our diagnostic hypothesis of a tubular defect causing urinary bicarbonate loss, likely associated with kidney sulfatide accumulation.

Based on this clinical experience, we prospectively started a blood and urinary acid–base balance monitoring in all subsequent patients, thus allowing prompt identification and correction of acidosis when needed, as what happened in the cases described below.

Patients from #2 to #6 showed a tendency to alkaline urinary pH (data not shown) and borderline low serum pH, bicarbonate and base

Table 1
Acute patients' characteristics. +/− indicates timing of the acute acidosis episode as respect to gene therapy (GT), where "Ch." stands for the day of initiation of chemotherapy and "Tx" indicates the day of transplantation of the gene corrected cells; d = days; hr = hours; mo = months. BM = bone marrow.

Patients	MLD variant	1st finding of acidosis		
		Age	Concomitant event	Before/after GT (or no GT)
1	Symptomatic EJ	5years	Sepsis	After Tx (+11 and +37 d)
2	Pre-symptomatic LI	15 ms	Febrile neutropenia	After (+9 d)
3	Pre-symptomatic LI	23 ms	Febrile neutropenia	After (+9 d)
4	Symptomatic EJ	11year	Main surgery (BM explant)	Before Ch. (−6 hr) and Tx (−4 d)
5	Pre-symptomatic LI	8 ms	Sepsis	Before Ch. and Tx (−2 mo)
6	Symptomatic EJ	7years	Main surgery (BM explant)	Before Ch. (−6 hr) and Tx (−4 d)
7	Late symptomatic LI	3.2 years	Status epilepticus	No GT