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RESEARCH REPORT

Vitamin B_{12} Administration by Subcutaneous Catheter Device in a Cobalamin A (cblA) Patient

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Abstract Cobalamin A deficiency (cblA) is an inherited disorder of intracellular cobalamin metabolism, caused by impaired 5′-deoxy-adenosylcobalamin (AdoCbl) synthesis. Hydroxocobalamin (OHCbl) is the cornerstone of cblA treatment because vitamin B12 may completely restore AdoCbl deficiency. Parenteral administration, intravenous, subcutaneous or intramuscular, is generally required to achieve effect. Daily injections represent a problem for the parents and the caregivers, and this may lead to poor compliance and scarce adherence to the long-term treatment.

Our report describes the case of a patient with cblA deficiency, diagnosed by newborn screening, positively treated with daily OHCbl administration by a subcutaneous injection port (i-port advanceTM). After the insertion of the device, we checked methylmalonic acid (MMA) levels weekly for the first month and then monthly. MMA level remained always in the normal range.

To date, placement of a subcutaneous catheter to minimize the pain related to parenteral vitamin B12 punctures has been described only in a patient with deficiency of the enzyme methylmalonyl-CoA mutase (MUT). No other experiences are described in the literature.

Our case shows that OHCbl administration using a subcutaneous catheter is safe and effective even in patients with cblA deficiency. The use of subcutaneous devices may reduce difficulties in providing parenteral daily injections which is the main reason discouraging physicians and families to use such an invasive treatment. Moreover, our experience may be translated to other inherited metabolic disorders, such as cobalamin C (cblC) disease, which may require daily parenteral drug administration.

Methylmalonic acidurias are a heterogeneous group of inborn errors of metabolism biochemically characterized by the accumulation of methylmalonic acid (MMA) in body fluids and tissues. Isolated methylmalonic aciduria may be caused by a complete or partial deficiency of the enzyme methylmalonyl-CoA mutase (MUT) or by a defect in the synthesis of its cofactor 5′-deoxy-adenosylcobalamin (AdoCbl), derived from vitamin B_{12}. Three inherited disorders of intracellular cobalamin metabolism are caused by impaired AdoCbl synthesis: cblA (OMIM 251100), cblB (OMIM 251110), and cblD-variant 2 (OMIM 277410) (Baumgartner et al. 2014; Merinero et al. 2008).

Most patients with isolated MMAuria present in the newborn period or infancy with acute deterioration of their general clinical condition, metabolic acidosis and hyperammonemia, evolving to coma and death, if patients are not treated. Initial acute management includes stopping protein intake and starting intravenous (IV) glucose. Combined treatment including parenteral L-carnitine, hydroxocobalamin (OHCbl), sodium benzoate, L-arginine, and N-carbamylglutamate should be given until a provisional diagnosis has been made (Baumgartner et al. 2014). OHCbl is the cornerstone of cblA treatment because vitamin B_{12} may completely restore AdoCbl deficiency and OHCbl, if available, is preferred over cyanocobalamin. Parenteral administration, IV, subcutaneous (SQ) or intramuscular (IM), is generally required to achieve effect. To date, the efficacy of oral OHCbl in MMA patients is still debated and yet not proved.

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Responsiveness to vitamin B_{12} should be carefully checked in all patients with MMA, because it may significantly influence the prognosis and may also suggest which complementation group the patient belongs to.

Long-term prognosis of MMAurias strongly correlates with vitamin B_{12} responsiveness, which is typically found in all cblA patients, and less commonly in cblB and MUT patients (Baumgartner et al. 2014).

Patients with cblA are usually treated in the long term with OHCbl 1–2 mg IM or SQ 1–7 times a week, but cobalamin dosage has to be adjusted to MMA excretion and clinical status in cobalamin-responsive patients. Long-term treatment includes also oral L-carnitine supplementation, and protein restriction (Grünewald et al. 2014).

Parenteral daily injections represent a problem for the parents and the caregivers, and this may lead to poor compliance and scarce adherence to the long-term treatment.

We report the case of a newborn presented at the second day of life with recurrent vomiting, lethargy, and poor general condition associated with a biochemical picture of metabolic acidosis (pH 7.24, pCO_2 16 mmHg, HCO_3 6.9 mmol/L, AG 33 mmol/L) and hyperammonemia (271 μmol/L). Newborn screening (NBS) results were available at 50 h of life and highlighted increased propionylcarnitine (C3 11.63 μmol/L, n.r. 0.60–3.30 μmol/L) and its ratios to free carnitine (C3/C0 0.78, n.r. 0.05–0.27) and to acetylcarnitine (C3/C2 0.4, n.r. 0.03–0.17). Heptadecanoylcarnitine (C17 0.3 μmol/L, n.r. 0.02–0.08 μmol/L) was also high. Second tier tests showed increased MMA (>200 μmol/L, n.r. <5 μmol/L) and methylcitric acid (6 μmol/L, n.r. <1 μmol/L), but normal homocysteine (Hcy).

Diagnosis of isolated MMA was confirmed by high MMA excretion in the urine (5,500 mmol/mol of creatinine) and normal plasma total Hcy level (7.6 μmol/L, n.r. ≤10 μmol/L).

While the confirmatory tests were carried out, we started detoxification therapy with sodium benzoate, carbamylglutamate, L-arginine, L-carnitine, and OHCbl, associated with a protein-free diet. We used IM OHCbl at the dosage of 1 mg/day. We observed in 48 h a dramatic reduction of blood and urine MMA levels. Plasma MMA levels decreased from 453.8 to 5.5 μmol/L. Also MMA values on dried blood spot (DBS) dramatically reduced in 3 days, changing from 429.5 to 6.55 μmol/L.

Vitamin B_{12}-responsive phenotype was confirmed by complementation analysis on fibroblasts, suggesting a defect of AdoCbl synthesis, in particular cblA deficiency. MMAA gene analysis identified two heterozygous mutations in MMAA gene (Allele 1: c.445_448del; Allele 2: c.733+1G>A).

The patient was treated with 1 mg of OHCbl (1 mg/mL solution) IM a day associated with L-carnitine and a protein content of 1.8 g/Kg/day, which represents safe protein level for age.

To simplify parents' administration of OHCbl and to reduce the patient discomfort of multiple injections, we utilized a subcutaneous injection port (i-port advance™). The dosage of OHCbl (1 mg/mL solution) remained the same and the drug continued to be administered once daily. The subcutaneous catheter was exchanged by the parents every 5 days.

After the insertion of the device, we checked MMA levels on DBS weekly for the first 2 weeks and then monthly.

MMA levels remained always in the normal range. The mean DBS MMA level was of 2.43 μmol/L (range 0.75–6.55 μmol/L) and 1.97 μmol/L (range 0.4–6.15 μmol/L) before and after the application route was changed, respectively.

The patient is now 5 months old, he is growing well, and his neurological development is normal. No acute episode of metabolic derangement occurred.

At present, the subcutaneous injection port is still well tolerated. Parents have been educated to use independently the device and to adopt precautions to prevent infections of the site of injection. Parents report no problem with the use of the device and are happy to reduce the pain of injections.

The experience on parenteral OHCbl treatment for inborn errors of metabolism derives mostly from cobalamin C (cblC) patients (Carrillo-Carrasco et al. 2011). In these patients parenteral OHCbl (IV, SQ, or IM) is the only form of cobalamin proven to be beneficial (Carrillo-Carrasco et al. 2011). Many centers manage infants by providing 1 mg of parenteral OHCbl daily, but in the long term the frequency of administration is usually decreased to minimize daily injections and the dose is frequently not increased to account for their weight gain. Although these practices are based on limited evidence, they may be responsible of providing progressively sub-therapeutic cobalamin serum levels, a possible risk factor for progression of complications in patients with cblC disease (Carrillo-Carrasco et al. 2011).

Placement of a subcutaneous catheter to minimize the pain related to parenteral punctures has been described only in a patient with MMA due to MUT (Freehauf et al. 2011). No other experiences are described in the literature. Nevertheless, there are some conditions, such as cblC, where using a subcutaneous catheter may be very useful in the long-term treatment.

Our case shows that OHCbl administration using a subcutaneous catheter is safe and effective even in patients with cblA deficiency. The use of subcutaneous devices may reduce difficulties in providing parenteral daily injections

which is the main reason discouraging physicians and families to use such an invasive treatment. Hopefully this practice will improve adherence and compliance in the long term.

Moreover, our experience may be translated to other inherited metabolic disorders which require daily parenteral drug administration.

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Compliance with Ethics Guidelines

Conflict of Interest

Evelina Maines declares that she has no conflict of interest.

Grazia Morandi declares that she has no conflict of interest.

Giorgia Gugelmo declares that she has no conflict of interest.

Florina Ion-Popa declares that she has no conflict of interest.

Natascia Campostrini declares that she has no conflict of interest.

Andrea Pasini declares that he has no conflict of interest.

Monica Vincenzi declares that she has no conflict of interest.

Francesca Teofoli declares that she has no conflict of interest.

Marta Camilot declares that she has no conflict of interest.

Andrea Bordugo declares that he has no conflict of interest.

All procedures followed were in accordance with the Helsinki Declaration of 1975.

Details of the Contributions of Individual Authors

Dr. Maines E and Dr. Morandi G conceived the study and wrote the draft. Dr. Ion-Popa F, Campostrini N, Pasini A, Vincenzi M, Teofoli F, and Camilot M performed biochemical analysis and ensured the accuracy of the data. Dr. Gugelmo G performed dietetic evaluation of the patient. Dr. Bordugo A revised the manuscript critically for important intellectual content.

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