Study of the effect of growth hormone treatment on growth in patients affected by the inherited metabolic disease methylmalonic acidemia

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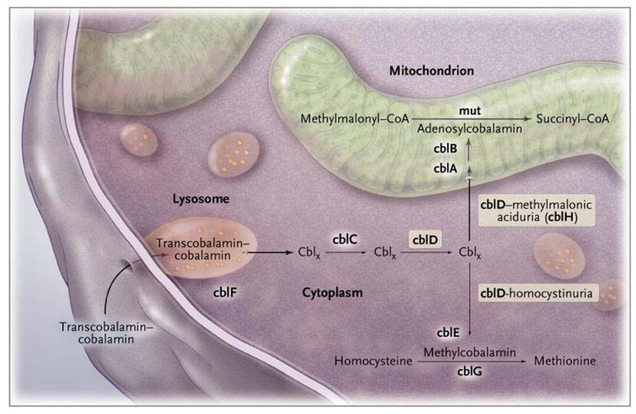
Background

Methylmalonic acidemia (MMA) is an inborn error of metabolism affecting the catabolism of the amino acids: valine, isoleucine (branched-chain aminoacids), methionine, threonine, and of cholesterol side chains, odd chain fatty acids. MMA is the most prevalent disorder of intermediary metabolism of aminoacids. Most patients present with systemic illness due to endogenous intoxication by MMA and other propionic acid metabolites (encephalopathy/coma, epilepsia, ataxia, metabolic acidosis, feeding problems, dehydration, vomiting).

A great problem in these children is that of a growth abnormality with progressive slowing of the statural growth rate, in contrast with a normal or even accelerated weight gain. These abnormalities are accompanied by bone demineralization and muscle hypotonia.

Objective and Hypotheses

We propose conducting a prospective study to determine the metabolic effects and effects on growth of 2 year treatment with recombinant human growth hormone (rhGH) in 5 children presenting with vitamin B12 non-responsive methylmalonic aciduria in the age group of 2-12 (prepubertal) age. Course will be assessed longitudinally with each patient acting as his/her own control. The primary goal of this study is that rhGH treatment, by increasing protein anabolism, enables an improvement in growth rate and a gain of at least 1 SD in 1 year. The secondary goal is that rhGH treatment improves metabolic equilibrium due to enhanced protein synthesis.



Intracellular cobalamin metabolism and Its defects
Coelho D et al. N Engl J Med 2008;358:1454-1464.

Methods

The children will receive rhGH at a dose of 0.05 mg/kg/day as a single subcutaneous injection daily, 7 days a week.

A glucagon test for GH should be performed since an important proportion of patients with organic acidurias suffer from partial or total GH deficiency.

The analysis will be conducted after 1 year.

If the treatment is shown to be effective, the children will be treated with rhGH for a further period of 1 year.

An extension should be provided for patients with a favourable response.

Inclusion Criteria

- children of age greater than 2 years and less than or equal to 12 years,
- prepubertal children (Tanner ≤ 2),
- children presenting with vitamin-resistant methylmalonic acidemia,
- informed consent from both parents for each patient.

Exclusion Criteria

- vitamin B12-sensitive forms of methylmalonic aciduria,
- moderate forms defined by a protein tolerance ≥ 5 g/d of natural protein between 2 and 5 years, ≥ 18 g/d of natural protein between 5 and 8 years and ≥ 20 g/d of natural protein between 8 and 12 years,
- serious forms in which tolerance is restricted to the minimum essential amino acid requirements consisting in a valine allowance ≤ 220 mg/d (3.0 g of natural protein),
- severe concomitant disease liable to affect growth and/or anabolism such as kidney failure (glomerular filtration ≤ 50 mL/min/1.73 m2), nephrotic syndrome, heart failure, liver failure, diabetes mellitus, endocrine disease, etc.
- known or suspected allergy to the trial product or related products,
- participation in other clinical trials

Treatment Conditions

1) Natural **protein intake** will remain unchanged throughout the study.
   - The intake of the supplementary amino acid mixtures must also remain unchanged throughout the study.
   - The intake of trace elements and minerals will be adjusted to the recommended allowances for the age.
   - The adjuvant treatments (carnitine, metronidazole, vitamins) will be prescribed by the attending physician before inclusion in the study. The dosages will remain stable throughout the study.
2) The **dietary regimen** (meals, continuous or discontinuous enteral nutrition, etc.) will be determined as a function of the requirements of each child prior to inclusion. Every effort will be made to stabilize the regimen throughout the duration of treatment.
   - In the event of a substantial change made necessary by a change in the child's condition, pursuit of the study will be reviewed on a case-by-case basis.
3) **Adjuvant medications**: all the adjuvant treatments will be authorized with the exception of prolonged corticosteroids (androgens or estrogens) and thyroid hormones.

Study Follow-Up

1) **Physical examination** conducted at time points -6, -3, 0, 1, 3, 6, 12, 18 and 24 months:
   a) Progressiveness of the disease
   Clinical: frequency and seriousness of the episodes of decompensation. The seriousness of acute decompensation will be scored using a seriousness scale.
   b) Growth parameters
   Weight and height, puberty stage (Tanner).
   c) Nutritional evaluation
   - Dietary inquiry: dietary diary over the 3 days preceding consultation,
   - BMI, bicipital and tricipital skin folds.

   d) Therapies
2) **Laboratory panel** conducted at time points -6, -3, 0, 1, 3, 6, 9, 12, 15, 18 and 24 months:
   Laboratory panel: plasma and/or urinary organic acid chromatography, urinary urea/24 h, urinary creatinine/24 h, propionylcarnitine or C3 (whole blood on filter paper), plasma fatty acids with an odd number of carbons.
3) **Standard follow-up panel** for the patients at time points -6, 0, 6, 12, 18 and 24 months:
   Nutritional panel: chromatography of plasma amino acids, free and total carnitine, total blood count, plasma electrolytes, urea, creatinine, albumin, calcium, calciuria (Ca/Creat in a morning sample), phosphorus, alkaline phosphatase, triglycerides, total cholesterol.
4) **Laboratory tests** at time points 0, 1, 12 and 24 months:
   a) Growth markers: plasma IGF-1 and plasma IGF-BP3,
   b) Glucose tolerance, fasting blood glucose and insulin,
   c) Bone metabolism markers: osteocalcin (plasma), urinary pyridoline and D-pyridoline (24-h urine),
5) **Bone age** determined by the Greulych and Pyle method on a left hand radiography at times 0, 12 and 24 months.

Management of Acute Decompensations

The treatment of intercurrent acute decompensation is left to the discretion of the physician attending the child.

The decision to pursue growth hormone treatment is left to the discretion of the investigator. The patient will be maintained in the study if any discontinuation of growth hormone treatment does not exceed 10 days.

The clinical and laboratory evaluations related the protocol are to be conducted in patients in a steady state. Therefore the programmed evaluations will only take place 1 month after return to the basal state.

Withdrawal from the Study

- Any (unexpected) adverse effect related to rhGH.
- Any major change in the basic treatment liable to interfere with the results of the study (e.g.: discontinuation of enteral nutrition, liver transplant).
- Any suspension of growth hormone treatment for more than 10 consecutive days.
- All withdrawals of a patient from the study will be the subject of a detailed written report.

Results

Proof of concept for therapy with rhGH in children with methylmalonic aciduria has already been achieved by several authors, the largest cohort has been treated in Paris where the primary end point unfortunately was not the stimulation of growth in these patients but rather focused on improvement of the metabolic parameters. One patient of ours has received rhGH according to the protocol described above and manifested improvement of growth of 2 cm during a period of 3 months.

Assessment Criteria

Main criterion: GROWTH

- growth rate in SD for the age,
- height in SD for the age,
- weight in SD for the age,
- plasma IGF1 and IGF-BP3,

Secondary criteria:

- plasma propionylcarnitine and urinary methylmalonic acid for methylmalonic academia,
- number of acute decompensations in the year,
- plasma fatty acids with an odd number of carbons,
- bone synthesis markers: plasma osteocalcin,
- bone resorption markers: urinary pyridinoline and D-pyridinoline

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Conclusion

Patients affected by Methylmalonic acidemia are prone to growth abnormalities. Therapy with rhGH of these patients is promising, but should be studied in a prospective manner in order to get guidelines in starting this adjuvant treatment in this particular patient population.

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Financial support: Scientific grant from Ferring and Pfizer

Poster Design: Dirk De Weerdt (www.ddwesign.be) Po647