Case Report

Growth failure in a girl with Fanconi syndrome and growth hormone deficiency

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Introduction

Idiopathic or primary de Toni-Debré-Fanconi syndrome (FS) is characterized by dysfunction of the proximal tubule. This leads to the urinary loss of bicarbonate, phosphate, glucose, potassium, amino acids and other substances. One prominent clinical feature of FS is a substantial delay in body growth [1]. Hypophosphataemia, disturbed vitamin D metabolism and metabolic acidosis are possible causes for growth retardation. Chronic hypokalaemia and extracellular volume contraction seem to be cofactors, while glucosuria and the loss of amino acids are less important [2]. Some authors believe that despite adequate replacement of the crucial electrolytes, bicarbonate and vitamin D, final height in the range of target height can rarely be reached [3,4]. However, this notion is contradicted by others who observe a catch-up growth to height SDS above −2 under supportive therapy in combination with non-steroidal anti-inflammatory drugs such as ibuprofen or indometacin [5].

Interestingly, most publications do not report data on IGF-I or IGFBP-3 serum concentration in patients with FS. Likewise, no patients presenting with a combination of FS and growth hormone deficiency (GHD) have been reported. Given the prevalence of idiopathic GHD, however, 1 in 4000 children with FS would be expected to suffer from both conditions [6,7].

We present a girl with FS who presented with growth failure as a consequence of idiopathic GHD and was, eventually, successfully treated with recombinant human growth hormone (rhGH).

Case

The girl first presented to the paediatric nephrology out-patient department of the University of Erlangen-Nürnberg at the age of 2.5 years for the evaluation of glucosuria and metabolic acidosis. At that stage her height was 88.1 cm (SDS −0.84 according to Reinken and van Oost [8]) (Figure 1) with a BMI of 15.1 (SDS 0.0 according to Rolland-Cachera et al. [9]). Mean target height as calculated from parental height was 165.8 cm (SDS 0.2). Biochemical analysis confirmed glucosuria (300 mg/dl) and metabolic acidosis (pH 7.31, base excess −5.9) and revealed aminoaciduria, a decreased tubular reabsorption of phosphate (0.57 mmol/ml; normal > 0.8 mmol/ml) and an increased fractional excretion of potassium (40.6; normal 11.0 ± 5.4). Intact serum parathyroid hormone (iPTH) was normal until GH therapy was started. Calculated creatinine clearance using the Schwartz formula was normal throughout the course of the disease. Underlying disorders such as cystinosis, galactosaemia, fructose intolerance and Wilson’s disease were excluded as causes for FS using appropriate biochemical tests. The patient received potassium, phosphate and sodium bicarbonate replacement therapy, maintaining adequate serum concentrations throughout the course of the disease.

Until the age of 7 years the girl’s height developed in parallel to the 20th percentile (SDS −0.88 at 7 years), before gradually declining to SDS −2.13 at the age of 11.5 years (Figure 1). Throughout this period, IGF-I and IGFBP-3 levels were normal. Height velocity over 1 year at the age of 11 years was 2.2 cm (SDS −2.38). At that stage, the girl had no pubertal development (Tanner stage 1). BMI was 17.7 (SDS 1.02). Her bone age (Greulich and Pyle) was retarded by 2.5 years (Figure 1). There were no radiological signs of osteopathy. Alkaline phosphatase and iPTH were normal (Table 1). Her karyotype was 46, XX. The patient was biochemically euthyroid and the tubular losses were appropriately replaced. The patient did not suffer from chronic diarrhoea and was not...
underweight in relation to body height, reducing the likelihood of intestinal malabsorption or maldigestion.

For the first time, however, IGF-I serum concentration was low (139 ng/ml; SDS −1.7) while IGFBP-3 remained at the 90th percentile. Subsequent GH stimulation tests revealed an inadequate response to insulin, arginine and clonidin (maximal increase of GH 3.7, 0.2 and 0.6 ng/ml, respectively; normal >10 ng/ml). Magnetic resonance imaging of the pituitary gland and hypothalamus was normal.

The patient was placed on 0.18 mg/kg body weight/week of rhGH injected subcutaneously every evening. However, rhGH therapy did not immediately result in catch-up growth (Figure 1). Interestingly, alkaline phosphatase and parathyroid hormone rose tremendously after the start of rhGH (Table 1). After initiation of treatment with cholecalciferol (12 ng/kg/day) and the increase of phosphate replacement (from 1.5 to 3 mmol/kg/day), hyperparathyroidism subsided and height velocity (over the past 8 months) rose to 9.0 cm/year (SDS 6.6). Her current height is 150.9 cm (SDS −1.93) (Figure 1). The dose of rhGH was kept constant. The patient’s pubertal stage is now Tanner 3.

### Discussion

We present the case of a girl with idiopathic FS suffering from GHD at the same time. To the best of our knowledge this is the first report demonstrating this coincidence. Before GHD was suspected, adequate control of the tubular electrolyte losses had been installed. The patient was not treated with an inhibitor of prostaglandin synthesis such as indometacin.

The diagnosis of idiopathic GHD was suspected because of pathological growth velocity, low IGF-I concentrations and bone age retardation and could be confirmed using independent GH stimulation tests. It was astonishing that GH deficiency could only be revealed 4 years after growth velocity started to decline. However, there was a regular check of IGF-I concentrations providing normal values throughout. It appears possible that GH secretion was still sufficient to provide hepatic IGF-I synthesis whereas the impact at the growth plate was already inadequate.

While the patient, as expected, only needed physiological GH replacement therapy, increased requirements of phosphate and cholecalciferol were observed. These requirements were most likely caused by the increased demand of the skeletal system to provide GH-induced growth. In fact, catch-up growth was not observed before an adequate replacement of phosphate and cholecalciferol had been installed.

Poor compliance with therapy always needs to be suspected in patients not achieving appropriate therapeutic responds. In our patient, however, we experienced prompt improvement or normalization of pathological biochemical parameters such as iPTH, alkaline phosphatase and serum phosphate as soon as medication was changed.

It is well known that catch-up growth under GH replacement leads to an increase of enzymes and other markers of bone mass turnover [10]. Hyperparathyroidism may be observed at the beginning of GH therapy that may also be associated with the risk of osteolysis. In addition, successful GH therapy necessitates an adequate supply of nutrients that allows for the synthesis of bone mass. Inadequate nutrient supply

### Table 1. iPTH, alkaline phosphatase and serum phosphate in a girl with FS and GHD

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>7.0</th>
<th>11.5 before rhGH start</th>
<th>11.8</th>
<th>12.2</th>
<th>13.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (ng/ml; normal 15–65)</td>
<td>37</td>
<td>94</td>
<td>441</td>
<td>269</td>
<td>69</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l; normal 180–500)</td>
<td>596</td>
<td>477</td>
<td>1506</td>
<td>1168</td>
<td>943</td>
</tr>
<tr>
<td>Serum phosphate (mmol/l; normal 0.8–1.5)</td>
<td>1.1</td>
<td>1.5</td>
<td>0.89</td>
<td>0.93</td>
<td>1.47</td>
</tr>
<tr>
<td>Calcium phosphate product (mmol/l²; normal 4.5–5)</td>
<td>2.7</td>
<td>3.6</td>
<td>2.2</td>
<td>2.2</td>
<td>3.6</td>
</tr>
</tbody>
</table>
not only prevents the adequate synthesis of IGF-I [11] but also impairs growth. Therefore, sufficient supply of the substances lost by the kidneys is crucial to provide catch-up growth in a patient with FS and GHD.

In summary, we present a girl with FS and GHD who did not achieve adequate catch-up growth before the increased demands of vitamin D and phosphate had been supplied.

Conflict of interest statement. None declared.

References


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