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De novo formation of neutralizing IGF-I antibodies during rhIGF-1 treatment in a girl with IGFALS deficiency as distinct adverse event interfering with growth promotion

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Conclusion/Discussion

IGFALS deficiency is a rare cause of GH insensitivity (GHI**).** Neither rhGH nor rhIGF-I stimulated growth in our patient with IGFALS-deficiency. Severe adverse events and lack of efficacy prompted us to stop rhIGF-I treatment. In addition to elevated total serum IGF-I, rhIGF-I antibodies were detected in serum during rhIGF-I treatment but neither before nor after withdrawal. The aetiology of the formation of rhIGF-I antibodies in this patient with IGFALS deficiency during rhIGF-I treatment remains obscure. We speculate that antibodies were neutralizing as rhIGF-I failed to stimulate growth, caused sustained elevation of serum IGF-I concentrations leading to intolerance without hypoglycemia or hypokalemia opposed to observations in other patients with SPIGFD treated with rhIGF-I.

Case presentation

We report a German girl with short stature who was born as 2nd child at 40 weeks of gestation (length 49 cm, SDS -1.2; weight 2950 g, SDS 0.2). Her Caucasian parents were unrelated and healthy (target height 168 cm, SDS 0.2). At 6 years of age she presented with short stature (104.8 cm, SDS -2.94; weight 16.3 kg, SDS -2.0, BMI 14.8 kg/m², SDS -0.4) and growth failure (height velocity (HV) 5.1 cm/year, SDS -1.67). Serum concentrations of total IGF-I (SDS -2.3), IGFBP-3 (SDS -7.7) and of stimulated GH (max. 7.69 ng/ml) were reduced. cMRT was normal. Height (SDS -3.31), HV (SDS -1.68) and serum concentrations of IGF-I and IGFBP-3 (SDS -2.5 and -9.1) remained low during growth hormone (GH) therapy for 18 month. Spontaneous GH secretion over night was elevated (12 hours sampling every 20 minutes: mean GH concentration 7.2 ng/ml, reference >3; 24 h area over0-line 174.79 ng/mlx24h, reference >80). ALS serum concentration was low (102 mU/ml; reference 705-1270). A novel compound heterozygous mutation of the IGFALS gene (chromosome 16, Exone2 was found: *IGFALS*p.Pro474Leu/p.Phe602Cys (2 missense mutations; in silco analyses predicted protein dysfunction).

rhIGF-1 treatment course

Therapy with rhIGF-1 was started with 2x40 µg/kg/d and gradually escalated to 2x120 µg/kg/d s.c. Serum concentrations of total IGF-I (Mediagnost, FRG), insulin, glucose and potassium were measured before and after rhIGF-I (30, 60, 120, 180 and 360 minutes) at times of dose adaptation. Headaches without papilledema, dizziness and leg pain were reported during follow up. Serum IGF-I were sustained elevated during rhIGF-I treatment course (Figure 1). Serum glucose and potassium were within reference ranges throughout but serum insulin was elevated. Treatment was stopped after 10 months as growth remained poor (**Δ**HSDS -0.26; HV SDS -0.94). Stored serum samples were than also screened for rhIGF-I antibodies (electrochemiluminescence assay, ECLA; Table 1).

Table 1

Serum rhIGF-I AB titer before, during and after rhIGF-I therapy

rhIGF-I dose/day	rhIGF-I AB titer
before rhIGF-I	<1:100
2x40µg/kg	1:400
2x80µg/kg	1:400
2x120µg/kg	1:2048
after rhIGF-I	<1:100

Figure 1

Repetitive serum IGF-I measurements before and after rhIGF-I (40, 80, 120 µg/kg s.c.) expressed as ng/ml (A) and SDS (B).