

The ALS dose matters? Response to human growth hormone treatment in patients with acid-labile subunit deficiency

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Conclusion:

In patients with an absolute deficiency of ALS, treatment with either GH or IGF-I might be without use. However, those patients with low but detectable IGF-I and ALS levels (heterozygous mutation), might profit from GH treatment. We speculate that the ALS dose could matter when weighing treatment options in ALS deficiency.

Background / Aims:

In patients with acid-labile subunit (ALS) deficiency, the inability to build ternary complexes result in a marked reduction of circulating total insulin like growth factor I (IGF-I). Height reduction by heterozygosity is about 1 SD in comparison to wild type. In homozygosity or compound heterozygosity a height loss of -2 to -2.5 SD occurs. This is suggestive of a gene-dosage effect. How does treatment with human growth hormone (GH) influence height development in relation to the underlying genetic defect and the ALS concentration?

Patient 1

- homozygous mutation (IGFALS p.Asn84Ser)
- undetectable ALS, BP-3 and IGF-I concentration: < 100mU/ml, < 50 ng/ml and <25 ng/ml, respectively
- age of 6.7 years and a height of -3.03 SD at first GH treatment under the diagnosis of NSD, bone age at 6 years (Figure 1)
- escalating doses of GH up to 0.05 mg/kg BW/day (18 months)
- Treatment with recombinant IGF-I up to 36 IU twice a day, 0,11mg/kg BW / day (13 months) (figure 2)

Patient 2

- heterozygous mutation (IGFALS p.Pro259Leu)
- low ALS, BP-3 and IGF-I concentrations:
 ALS 189 mU/ml (normal range 986-1678 mU/ml),
 BP-3 290 ng/ml (normal range 337-1024 ng/ml),
 IGF-I 139 ng/ml (normal range 250-1060 ng/ml),
 respectively
- age of 15.5 years and height of - 1,9 SD at start of GH treatment after exclusion of GHD, bone age at 13,8 years. (figure 3)
- escalating doses of GH up to 0.03 mg/kg BW/day (22 months)

Results

- ✓ **Patient 1** did not profit from treatment with GH or IGF-I and showed no increase in height-SD. No change in IGF-I levels throughout either treatment. Near final height was -3.0 SD.
- ✓ **Patient 2** with low, but detectable IGF-I and ALS levels improved height during GH treatment as well as final height: -0,4 SD. During GH treatment IGF-I levels increased.

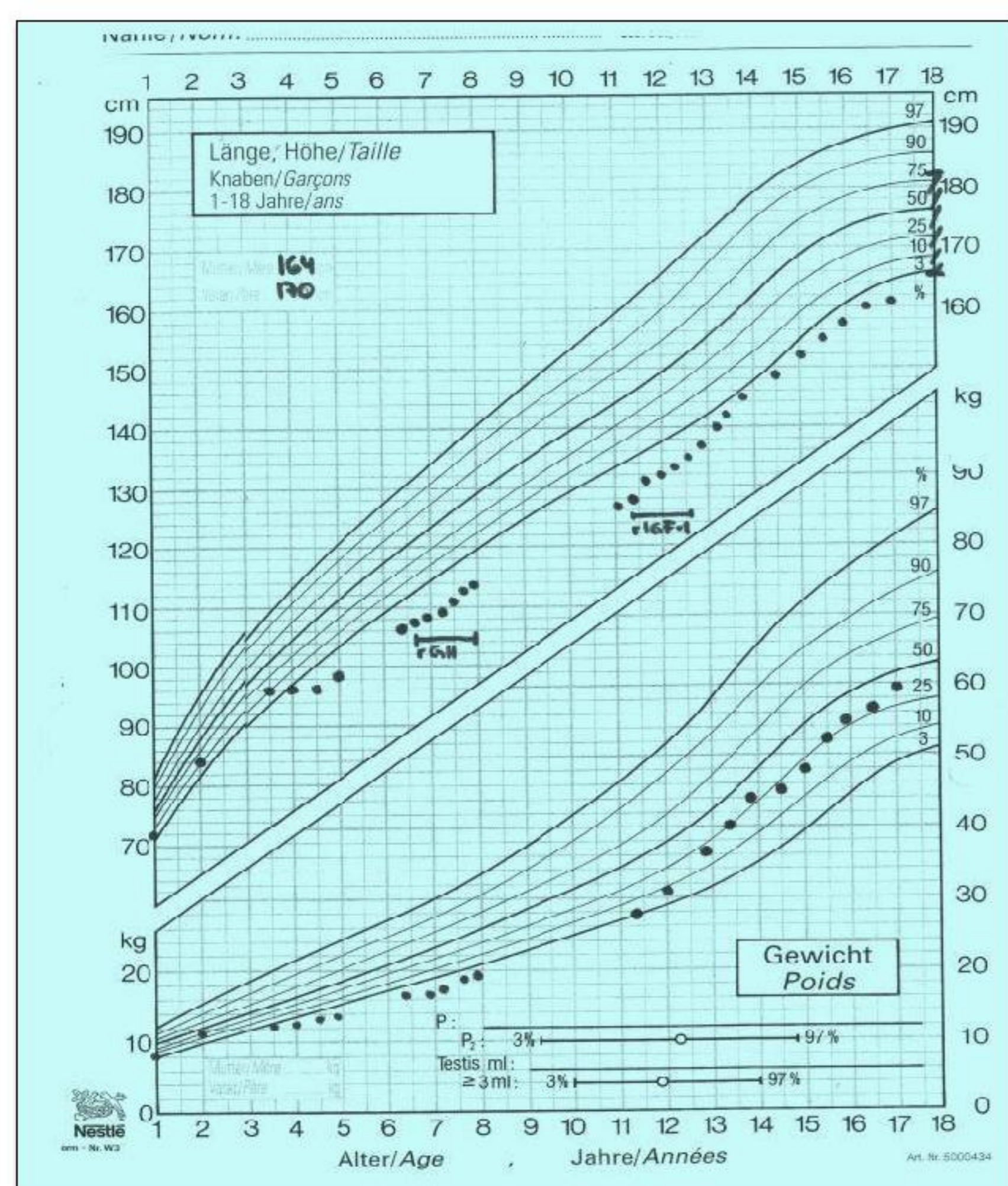


Figure 1 & 2: Growth chart and IGF-I kinetic in patient 1

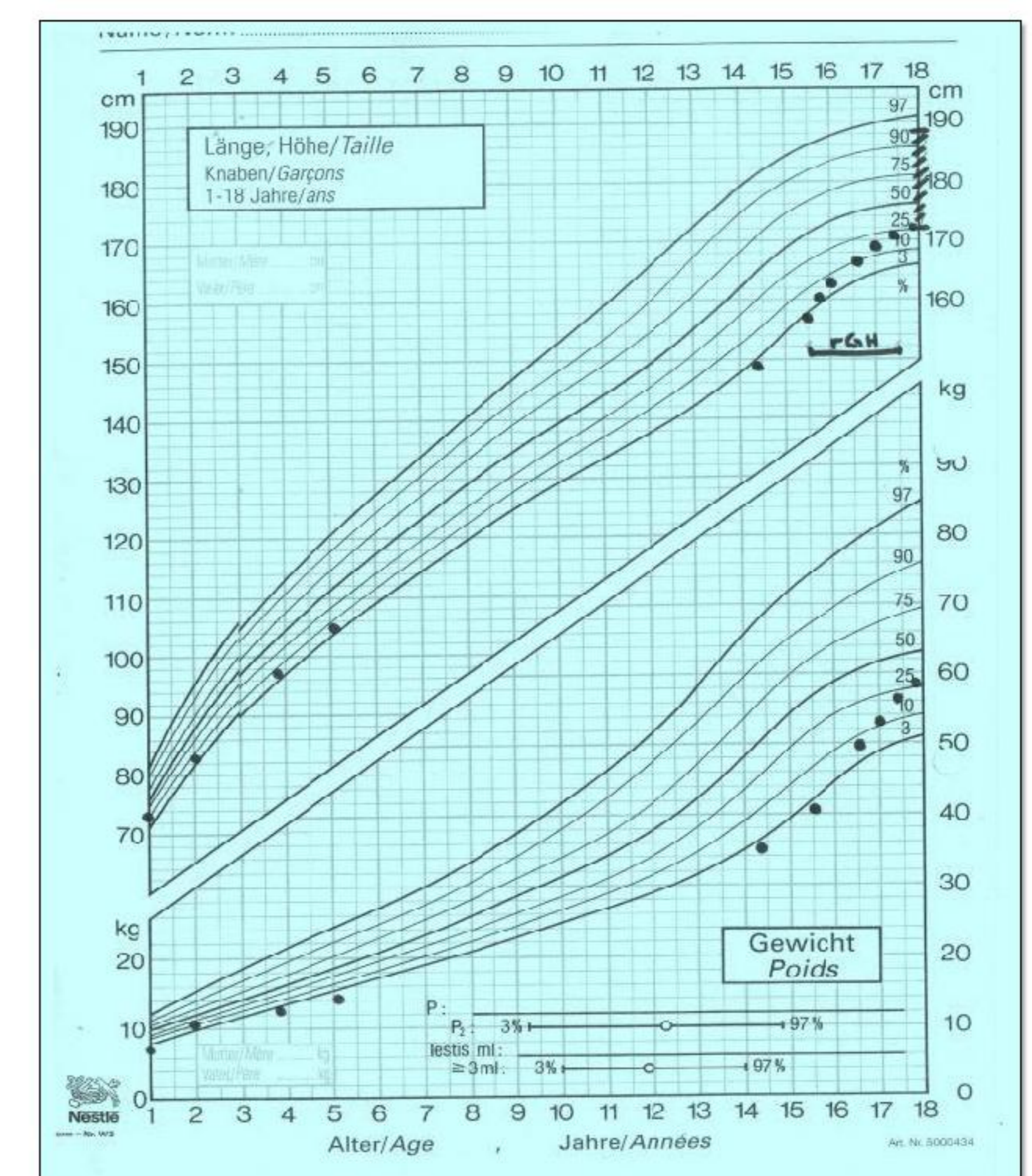
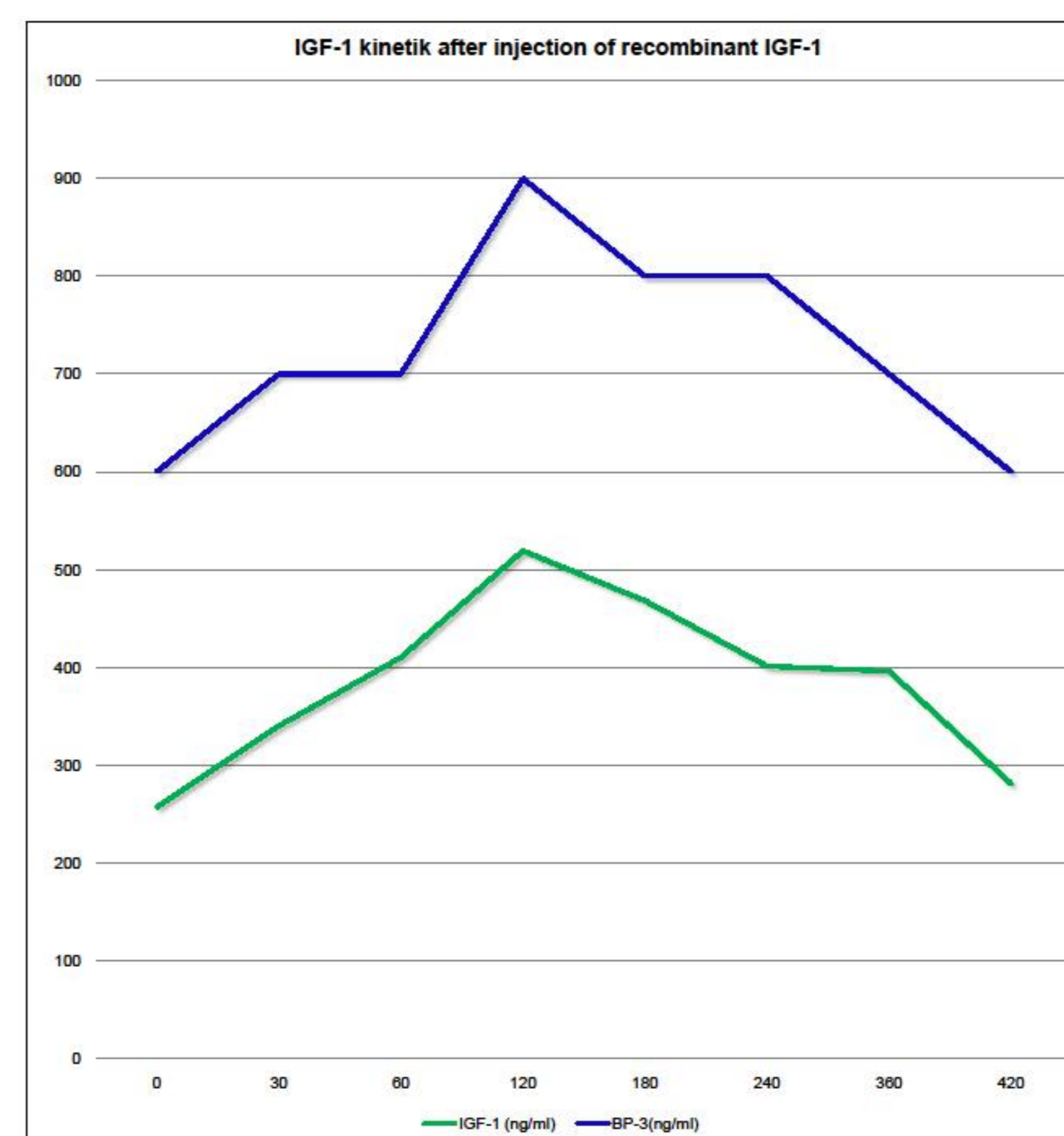


Figure 3: Growth chart of patient 2

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