

# Response to growth hormone therapy with high IGF-1-levels and severe insulin resistance in two-cases with a novel homozygous mutation in POC1A

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## BACKGROUND

- SOFT-syndrome (#MIM 614783) is a rare condition characterized by short stature, onychodysplasia, facial dysmorphism and hypotrichosis caused by *POC1A* gene mutations. Moreover, severe insulin resistance (IR) and metabolic disorders may also accompany. Hereby, we report two-patients with SOFT-syndrome, who had severe short stature and IR, with a novel *POC1A* mutation.

## CASE REPORTS

- Patient 1 (P1), a 18-month old girl and Patient 2 (P2), a 32-month old boy were referred with growth retardation. P1 was born at full-term to consanguineous parents, and P2 was born at 35th gestational week (GW) to unrelated parents. Both of them were born SGA. Their anthropometric measurements and physical examination findings at referral are shown in Table 1. Laboratory tests for chronic and metabolic diseases were normal. central hypothyroidism was detected in both patients. Sella MRI was normal; there was no adrenal insufficiency and LT4 (12.5 µg/day) was started.
- At follow-up, growth velocities (GV) were low in both patients. Growth hormone (GH) stimulation tests were performed and responses were insufficient. GH treatment was started in P1 and P2 with doses of 42 and 27.5 µg/kg/day, respectively. Both patients required dose adjustments for high IGF-1-levels (mean IGF-1-SDS: 5.7&5.6, respectively).
- On GH treatment, extremely high insulin-levels were observed. OGTT was performed. While P1 had impaired glucose tolerance (2nd-hour-glucose: 163 mg/dL) and severe IR (total-insulin: 2600µU/mL), P2 had only severe IR (total-insulin>2700µU/mL). Additionally, hyperlipidaemia was remarkable in P1. While P1 received both of metformin and atorvastatin, P2 received only metformin.
- As puberty progresses, GV decreased and GH treatment was discontinued at the 4th-year in P1. In P2, the change in height SDS was better than P1, therefore it has been continued in P2. Last clinical findings of patients are detailed in the Table 1. WES analysis revealed a novel homozygous mutation (p.Leu244Pro) in the *POC1A* gene in both patients.

## CONCLUSION

- A novel pathogenic variant in the *POC1A* gene was detected, which explained primordial dwarfism, dysmorphic findings and severe IR in both patients.
- A partial improvement on height SDS were with GH therapy. High IGF-1 levels on GH treatment were also associated with IR. It was also speculated; hyperinsulinemia may also have contributed to the increase in height SDS during the prepubertal period.

Table 1: Anthropometric measurements and clinical findings of patients during follow-ups

|                             | P1   |                      |                          |                       | P2   |                 |              |                           |
|-----------------------------|--|----------------------|--------------------------|-----------------------|--|-----------------|--------------|---------------------------|
| Age (yrs)                   | 18 months (At presentation)  | 5 4/12 (Onset of GH) | 9 3/12 (Cessation of GH) | 14 (Last Examination) | 2 8/12 (At presentation)   | 6 (Onset of GH) | 6 9/12       | 9 8/12 (Last Examination) |
| Weight kg/(SDS)             | 4.5/(-6.3)   | 11.8/(-3.6)          | 20.5/(-2.2)              | 30.9/(-4.3)           | 11.3 /(-1.9)   | 18.2/(-0.9)     | 18.2/(-1.6)  | 28.7/(-0.5)               |
| Height cm/(SDS)             | 59.8/ (-6.4)   | 85.2/(-5.6)          | 108.7/(-4.2)             | 116/(-7.5)            | 77.1 (-4.3)  | 95.1 (-4.3)     | 102.8(-3.5)  | 118.2/(-3.0)              |
| Head circumference cm/(SDS) | 43.1/(-2.9)  | 46.5/(-2.9)          | 47.6/(-3.3)              | 49.1/(-4.6)           | 46.8 (-2.0)  | 48.8 (-2.1)     | 48.9(-2.1)   | 49.9/(-2.4)               |
| BMI kg/m <sup>2</sup> (SDS) | 12.7/(-3.4)  | 16.03/(+0.5)         | 17.4/(+0.3)              | 22.9/(+0.8)           | 19 (+1.8)  | 20.1 (+2.3)     | 17.2 (+0.9)  | 20.5(+1.3)                |
| SH/Height                   | 0.76   | 0.63                 | 0.58                     | 0.57                  | 0.56   | 0.57            | 0.57         | 0.54                      |
| Puberty                     | B1/1 P1  | B1/1 P1              | B2/2 P2                  | B5/5-P3               | TV 1mL/1mL   | TV 2mL/2mL      | TV 2mL/2mL   | TV 3mL/3mL                |
| Bone Age (yrs)              | -  | 4                    | 10-11                    | 18                    | -  | 6               | 10           | 13                        |
| PAH cm/SDS                  | -  | -                    | 122.9 (-6.8)             | -                     | -  | -               | 131.1 (-7.3) | -                         |
| Target Height cm/(SDS)      | 160.8/(-0.4)   |                      |                          |                       | 179.2/(+0.5)   |                 |              |                           |
| Dysmorphic findings         | Myopia, blue sclerae, deeply set eyes, prominent forehead, pointed chin, gingival hypertrophy<br>Fetal fingertip pads and bilateral clinodactyly of the 5th fingers, brachydactyly, small and puffy hands and feet, hallux valgus tall vertebral bodies, good communication skills, adequate school performance<br>S-shaped scoliosis with the upper curve convex to the left, narrow pelvis, and narrow iliac wings |                      |                          |                       | bitemporal narrowing, hypertrichosis on frontotemporal regions periorbital fullness, short palpebral fissures, bilateral epicanthal folds, bilateral strabismus, brachydactyly, small and puffy hands and feet, broad thumbs and halluces, genu recurvatum, S-shaped scoliosis with the upper curve convex to the left, narrow pelvis, and narrow iliac wings, increased radiolucency of phalanges, platyspondyly high-pitched voice, hyperactive behavior |                 |              |                           |

