

# Growth hormone deficiency in a case with Neurofibromatosis-Noonan Syndrome (NFNS)

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## OBJECTIVES

NFNS is a distinct entity which has variable features of both NF1 (neurofibromatosis type 1) and NS (noonan syndrome). The genetic studies suggest that NFNS originates from different mutations at distinct genes affecting a common intracellular signal transduction pathway called RAS-MAPK pathway. This pathway plays roles in cell proliferation, differentiation, and apoptosis.

The number of effected genes in the RAS-MAPK pathway and the diversity of the mutations in these genes result in various different phenotypic characteristics and different syndromes. Since these syndromes are associated with the effects on the same pathway, they are called "RASopathies" or RAS-MAPK syndromes. NFNS is an important RASopathy and the mutations in the NF1 gene are the major genetic reasons underlying NFNS.

Growth hormone deficiency (GHD) has been relatively frequently identified in NF1 and NS, however GH (growth hormone) treatment in NFNS is still a matter of debate. The case presented herein is important, as it represents the outcomes of GH therapy in NFNS.

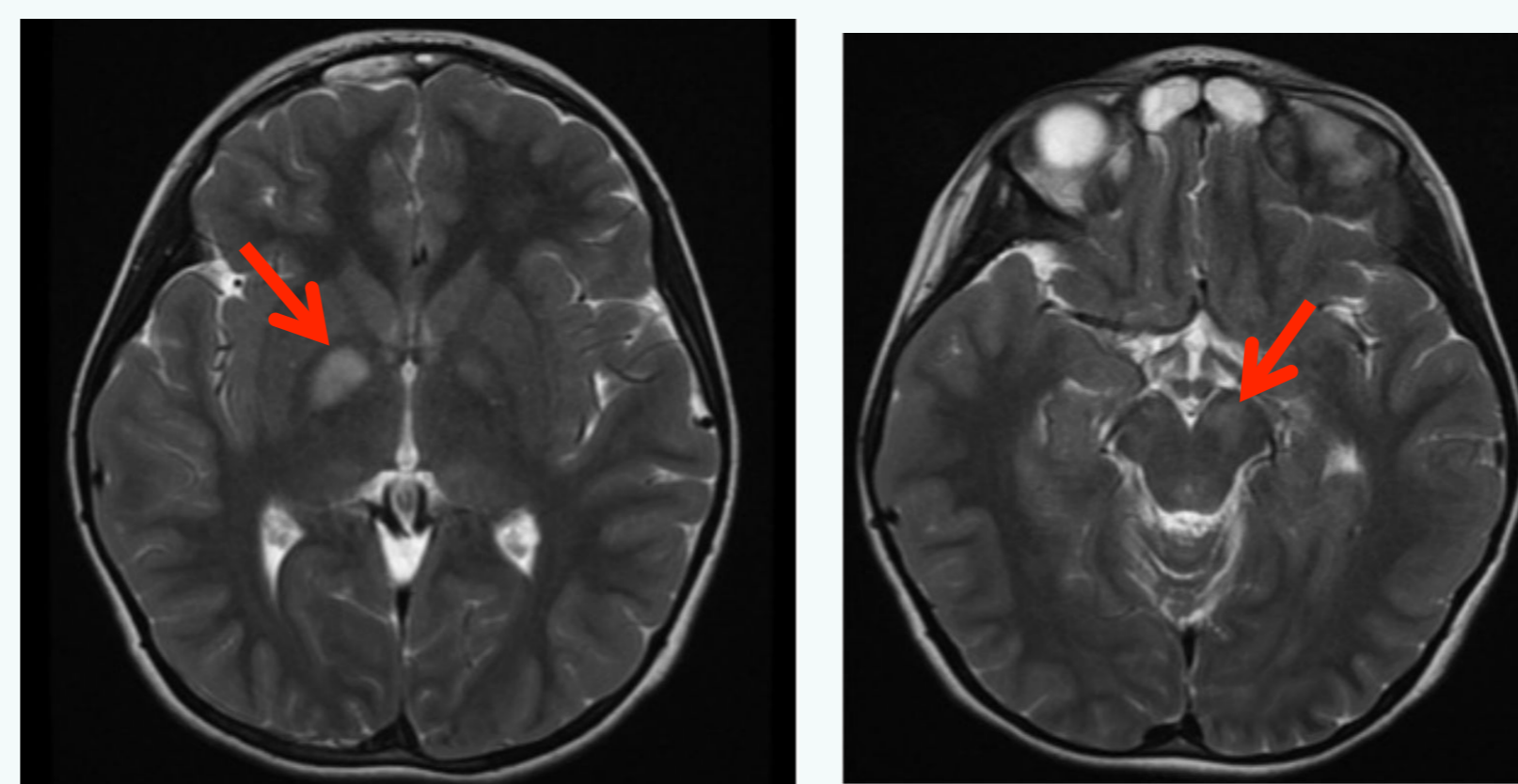
## METHODS

A 13-year-old girl presented with short stature having the features of NFNS and fulfilling the criteria of GHD is presented. There was no underlying reason, such as severe skeletal deformities, suprasellar lesions, or nutritional deficiency to rationalize the short stature observed.

The father also had features representing both NF1 and NS. The genetic analysis of the patient and the father both revealed a truncating mutation in the NF1 gene c.7846C>T(M82814), p.Arg2616X (AAA59924). This mutation is indeed a mutation that is seen in classical NF1 cases.

### Cranial MRI of the patient

Lesions of NF in cerebral peduncles and globus pallidus, hypoplastic pituitary gland



At admission

Height SDS: -4.4

Height velocity: -3.4

Peak GH in stimulation tests: 3.9 ng/ml

IGF1 and IGFBP3 SDS levels <-3

Other pituitary hormone levels: Normal

The patient fulfilled the criteria of

GHD, GH therapy was initiated

## Physical examination of the patient



### Features suggestive of NF1

- Multiple café-au-lait spots
- Axillary freckling
- Relative macrocephaly

### Dysmorphic facial features suggestive of NS

- Short and webbed neck
- Low posterior hairline
- Cubitus valgus
- Brachy-clinodactyly
- Widely spaced nipples

Her pubertal stage was Tanner stage 2.

Karyotype analysis was 46,XX.

## RESULTS

At the beginning of GH therapy

Height SDS: -4.3

Predicted Adult Height SDS: -4.0

Midparental Height SDS: -3.5

Height velocity

1<sup>st</sup> year : 11.8 cm

2<sup>nd</sup> year: 8 cm

3<sup>rd</sup> year: 4.5 cm

At the end of GH therapy

Bone age: 14.5 years

Final Height : 147 cm

Final Height SDS: -2.7

GH therapy resulted in 1.3 SDS gain in the final height.

The GH dose (0.3 mg/kg/week)

was higher than the dose in idiopathic GHD, similar to the dose in Turner syndrome

Any significant side effects under GH therapy was not seen

## CONCLUSIONS

- There is limited experience with GHD in NFNS cases, since NFNS alone is a rare disease that is clinically difficult to identify.
- The case presented herein is important since it involves the co-occurrence of GHD and NFNS, has clinical manifestation in addition to a mutation in the NF1 gene, and to the best of our knowledge it is the first case in literature that represents the outcomes of GH therapy.
- Based on this case, it may be argued that short stature is a feature of NFNS; however, in some cases it can be caused by GHD and patients with NFNS who are not growing sufficiently, especially those without a known underlying reason to explain the short stature should be evaluated for GHD.
- GH therapy may be beneficial in patients with NFNS who are diagnosed with GHD.

## References

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