Puberty spectrum in neurofibromatosis – case reports

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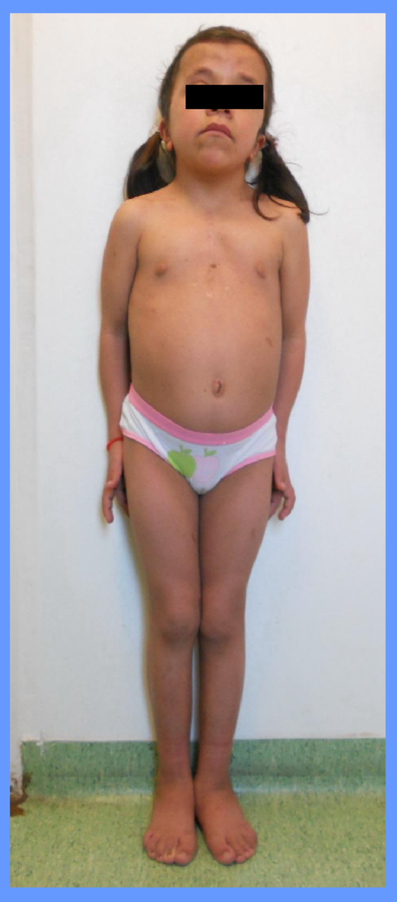
Neurofibromatosis 1 is a rare autosomal dominant disease determined by mutations in the RAS-MAPK pathway, frequently in the neurofibromin gene (NF1) on chromosome 17q11.
The NF1 protein, neurofibromin, is involved in control of cellular growth and differentiation through the interaction of its GAP related domain with p21ras and tubulin. In the presence of a mutation, Ras is uncontrolled leading to rapid cell proliferation and tumor formation.
Neurofibromatosis 1 phenotype can be more or less severe, including a form that associates the stigma of Noonan Syndrome. It can cause precocious or delayed puberty.

Case 1

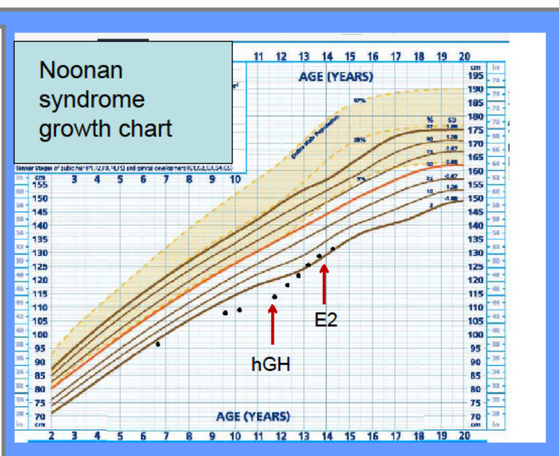


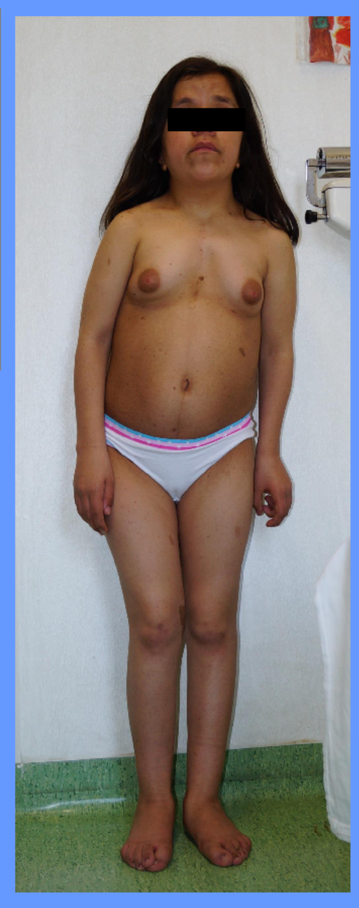
11 years 9 months

A 11years 9 months old girl known with Neurofibromatosis – Noonan Syndrome (NF-NS) was admitted for severe growth deficit (-5.14 SDS).
She had over 20 café au lait spots, hypertelorism, pterigium colli, axillary and inguinal freckling, Lisch nodules, B1 P1.
At 18 months she had had surgery for pulmonary stenosis and after that a left ventricular tumor proved to be neurofibroma at biopsy.

She had low IGF1, normal thyroid function and empty sella on MRI. Her bone age was 8. hGH therapy (with 0.033 mg/kg/day) started with satisfactory results.

After 2 years, at a bone age of 13 she showed no signs of puberty.
A triptorelinum test was negative (basal LH – 0.10 mIU/mL; after triptorelinum LH – 4.29 [cut off 6]).
She was diagnosed with delayed puberty and estrogen was started with good results.



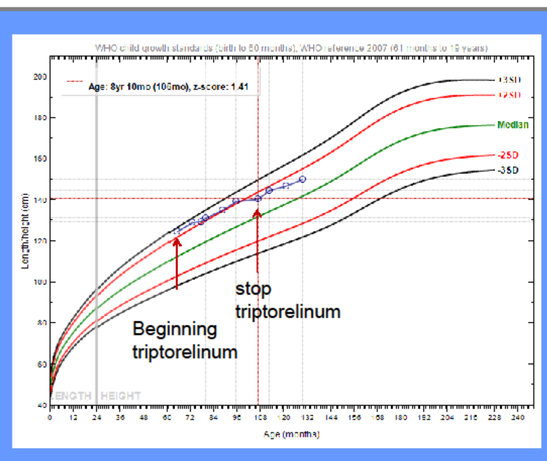


14 years 5 months

Case 2:

A 5 years old boy was admitted for pubertal evaluation. The clinical exam showed a tall child (+2.55 SDs) with over 10 large café au lait spots and subcutaneous neurofibromas. He was G4 P2 with a 25 ml total testicular volume.
A triptorelinum test confirmed central precocious puberty (basal LH – 2.85 mIU/mL, after triptorelinum 21.89 mIU/mL).
Bone age was 10. The cerebral MRI showed multiple neurofibromas and a hamartoma in the third ventricle. He was diagnosed with NF1 and central precocious puberty. Treatment with triptorelinum was started.

At 7 years he presented a seizure and a MRI showed an infiltrative tumor in the right thalamus. The biopsy showed a pilocytic astrocytoma. Radiotherapy and chemotherapy were started and continued for 18 months with monthly iv treatment. The evolution was favorable and a MRI after the completion of treatment showed no residual tumor



At the age of 9.6 years treatment with triptorelinum was stopped and puberty resumed. He was 1.2 DSD with a bone age of 13

Conclusions:

NF1 can cause all types of pubertal abnormalities and patients should be monitored closely. NF1 patients have an increased risk for tumor formation due to hyperactivation of the proto-oncogene RAS, an increased incidence of diencephalic syndrome, GH deficiency or GH hypersecretion, pheocromocytoma. Monitoring should be long term, because other complications of the disease can become apparent with time