A long follow-up in a young patient with Atypical Progeroid Syndrome

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Background

Atypical Progeroid Syndrome (APS) is a new AD laminopathy with phenotype and evolution probably depending on the mutation.

The LMNA gene encodes lamin A/C, intermediate filament proteins associated with the inner nuclear membrane.

Mutations in LMNA gene cause a wide range of human diseases called "laminopathies" including cardiac disorders and/or muscular dystrophy, lipodystrophy or progeroid syndromes.

The group of progeroid syndromes includes: Hutchinson-Gilford progeria syndrome (HGPS), Mandibuloacral Dysplasia (MAD) and APS.

Clinical Report

We report a female patient arrived at our attention at 9 years and followed-up for 10 years.

At 9 yrs (Fig. 1) she showed: normal auxological and pubertal parameters; prominent eyes, beaked nose, high-arched palate, lower jaw overcrowding; retrognathia, sclerodermatous skin, sclerodactyly, type A lipodystrophy, distal fingers hypoplasia and mild hepatic steatosis.

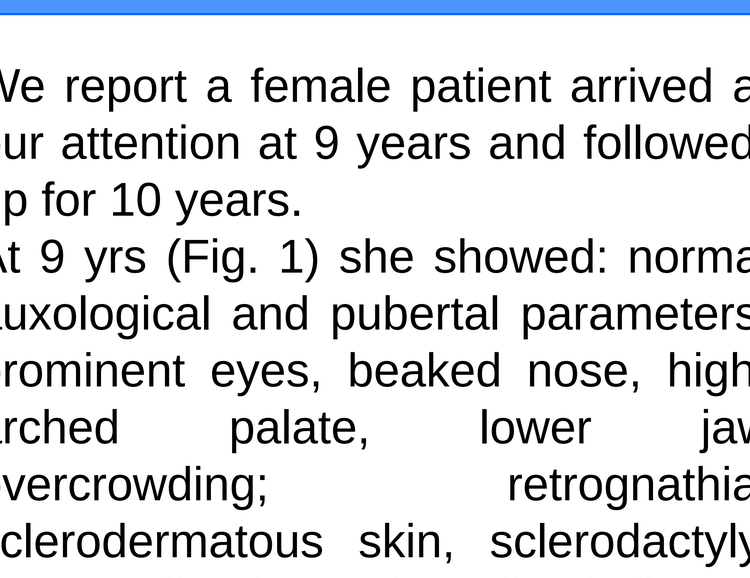

Fig. 1

LMNA gene analysis showed a de novo P4R heterozygous missense mutation.

After 10 yrs of follow-up (Fig.2), she showed: minimal breast development, mild signs of insulin resistence, increase in type A lipodystrophy, more evident sclerodermatous skin and retrognathia.

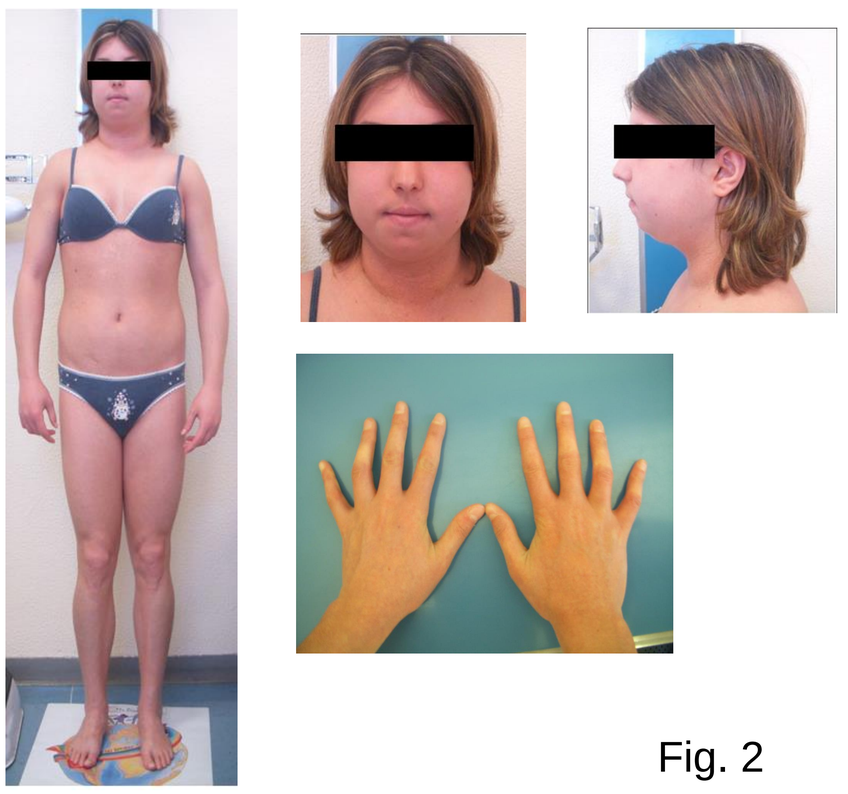

Fig. 2

Progerin, the alternatively spliced prelamin A form found in HGPS, was not detected in APS cells even at passage 5.

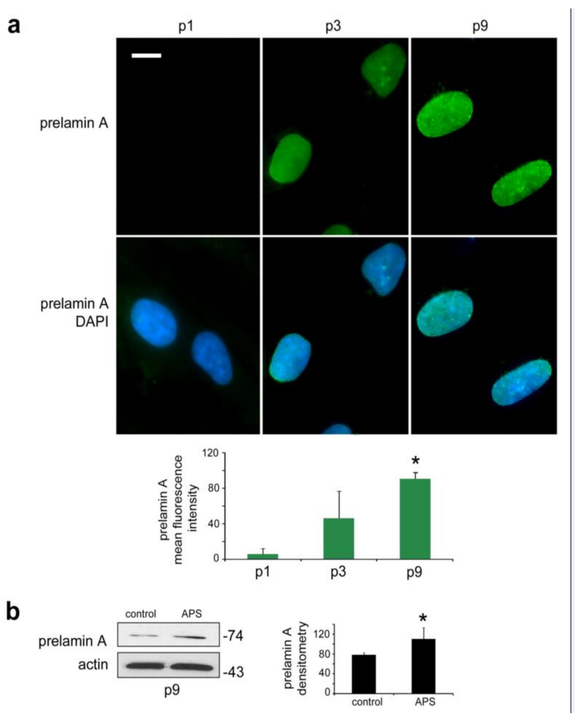

Fig. 3

At diagnosis, levels of prelamin A were measured in patient cells from oral esfoliate and the protein was undetectable. A skin biopsy was performed at age 14 and fibroblast cultures were established. While prelamin A was not detected at passages 1-3 in culture, prelamin A levels comparable to MAD were measured by western blot analysis in lysates of fibrobalsts at passage 5 (Fig. 3).

Moreover, we observed that cells subjected to stress conditions tended to form senescence associated heterochromatin foci, a hallmark of cellular senescence (Fig. 3)

Conclusions

Given the rarity of APS, it is important to recognize the clinical signs in the pediatric age in order to be able to formulate the diagnosis.

A precocious diagnosis permits an adequate follow-up with the possibility of controlling the evolution of the disease.

An inter-disciplinary follow-up (metabolic, cardio-vascular, dermatological, audiological and odontoiatric) is very important .

An adequate food survey with a personalized diet is important to control the metabolic disease.

In patients with P4R mutation lipodistrophy seems to be precocious and metabolic disease appears in adulthood.

Phenotypical signs seem to be milder than in other APS conditions.

At the moment P4R mutation is the only mutation reported in APS with an autosomal dominant fashion.

References

Garg A et al. J Clin Endocrinol Metab 94(12):4971-4983.).