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Premature ageing in two siblings: a case report of Hutchinson-Gilford progeria syndrome from rural Punjab, Pakistan

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Case Report

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Abstract

Objective: To present a rare case of Hutchinson-Gilford progeria syndrome (HGPS) in two siblings from a rural area of Punjab, Pakistan and discuss the clinical features along with the problems encountered in the diagnosis of the syndrome in this region.

A 4 years old girl and her 1-year-old brother were admitted to Tehsil Headquarters Hospital Mailsi with a history of one week of cough and fever. Children both had the classic dysmorphic appearance of HGPS with craniofacial disproportion, prominent scalp veins, alopecia, loss of eyebrows and eyelashes, proptosis, a narrow nasal bridge, thin lips and mandibular retrusion. The cardiovascular examination in the girl was normal and in the boy a pansystolic murmur was present. A leucocytosis with left shift was found and chest X-rays showed bilateral bronchopneumonic consolidation. HGPS diagnosis was made on clinical basis.

Conclusions: Though very rare, HGPS occurring in siblings emphasizes the need to identify progeroid characteristics in childhood. It is important for clinicians in low resource areas to be aware of this syndrome so as to be able to make early diagnosis and counsel the family.

INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS) is a very rare, life-threatening genetic disorder of the genes that govern normal cell aging that causes a child to grow up aging much faster. Estimated incidence is 1–4 to 1–8 per 1,000 live births, [1] and the mean life expectancy is about 14.6 years, [2] most of which are due to cardiovascular complications.

The cause of HGPS is a de novo point mutation in the LMNA gene located in exon 11 (c.1824C > T; p.Gly608Gly), which creates a cryptic splice site in the gene and leads to the production of a shortened, toxic version of Lamin A protein known as progerin. Progerin builds up in the nuclear envelope, leading to structural instability in the nucleus, DNA repair defects and premature cellular senescence.[3]

The early signs, which usually give the clue to clinical diagnosis, are disproportionately small face in relation to the calvarium, alopecia, subcutaneous fat loss, prominent veins in the scalp, and sclerodermatous skin changes.[4] The leading cause of morbidity and mortality is CVD, especially accelerated atherosclerosis. Throughout, intelligence and neurodevelopment are normal.

It is very unusual if more than one sibling in a family has HGPS. Two affected siblings from a family were seen in a district-level hospital in Mailsi, Punjab, Pakistan, which does not have a specialist paediatric genetics service, and this is highlighted by this case.

CASE REPORT

The Index case is patient 1, a female child aged 4 years.

A 4 year old girl presented to the Out Patient Department (OPD) of the Tehsil Headquarters (THQ) Hospital Mailsi, Punjab with a condition of productive cough associated with high grade, continuous fever for 1 week which responded to antipyretics intermittently. Cough started abruptly, was more severe at night and often was followed by post-tussive vomiting. Her parents complained of frequent respiratory tract infections from infancy. Permission for publication from the parents was sought.

A general examination showed that the child was dysmorphic and small for dates. Craniofacial examination showed a disproportion between the head and the face, enlarged calvarium, prominent scalp veins, complete scarring of the scalp, loss of the eyebrows and eyelashes, bilateral proptosis, nasal bridge flattening, thin lips and mandibular retrusion. The skin was very thin and taut, with no subcutaneous fat. These features were consistent with the classical phenotype of HGPS.

Examination of the thorax revealed tachypnoea, bilateral crepitations and auscultation. The examination of the cardiovascular system was normal. Abdominal examination failed to reveal any organomegaly.

Lab tests showed an increased white-cell count, with an increased percentage of neutrophils with a left shift, characteristic of an acute bacterial infection. Bilateral patchy opacities were seen on chest radiograph consistent with bronchopneumonia. She was started on appropriate antibiotic and supportive therapy.

Patient 3 — Child of patient 2 (male, aged 6 months)

Concurrently, the patient's 1-year-old brother was assessed, and he had a similar history of being ill for one week, with cough and fever. Physical examination revealed phenotypic characteristics very similar to his sister: craniofacial disproportion, prominent scalp veins, alopecia, loss of eyebrows and eyelashes, proptosis, narrow nasal bridge, thin lips and retrusion of the mandible. These results also confirmed HGPS in this sibling.

On cardiovascular examination, a pansystolic murmur was heard Grade III/VI loudest at the left lower sternal border, which is suggestive of a ventricular septal defect or atrioventricular regurgitation. This finding was not seen in the index case. Examination of the respiratory system also showed tachypnea and bilateral crepitation. A chest radiograph revealed bilateral bronchopneumonic changes. Laboratory investigations revealed leukocytosis with a left shift.

Children were treated with intravenous antibiotics, antipyretics and supportive respiratory care. However, genetic testing for LMNA mutation was recommended, but not performed, because of limited availability of molecular diagnostic facilities. Advise was given to the family about the syndrome and the importance of the cardiac findings in the younger sibling who was referred for echocardiographic and paediatric cardiology review.

DISCUSSION

The cases described in this report are unusual in two respects: first because they occurred in two biologically related children; second, because they were seen in a low income district-level hospital where the syndrome had not been seen before. The majority, if not all, HGPS cases are de novo mutations of LMNA, and the disease is not thought to be familial – but a few cases have been reported in the literature as a result of germline mosaicism.[6]

In both children the clinical diagnosis was simple due to the pathognomonic association of craniofacial dysmorphism, alopecia, proptosis and sclerodermatous skin changes in young children with recurrent infections and failure to thrive. The lack of cardiovascular disease in the older sibling and its presence in the younger sibling is consistent with the progressive nature of the atherosclerosis associated with HGPS and may represent age related differences in the severity of the disease.[7]

Bilateral bronchopneumonia was detected at presentation and is consistent with previously reported cases of HGPS.[4] This is thought to be related to reduced chest wall compliance and decreased respiratory reserve associated with the sclerodermatous changes and musculoskeletal involvement known to occur in HGPS.

Lonafarnib is an inhibitor of farnesyltransferase that has been proven to prolong a child's life and is the only medication approved by the United States Food and Drug Administration to treat HGPS. Availability in Pakistan is very low and this shows the contrast in accessibility to therapy of ultra-rare diseases in LMICs.

In familial HGPS, genetic counselling is very important. Gonadal mosaicism should be explained to parents as a theoretical risk of recurrence and molecular testing should be offered to future pregnancies. Optimally managing this requires a multidisciplinary approach with paediatrics, cardiology, dermatology and genetics.

CONCLUSION

The presence of two siblings within a family's history with HGPS is a rare and very significant occurrence. The highlight of this report is the need to be aware of progeroid syndromes by the clinician in a resource-restricted setting, where early clinical diagnosis, counselling of the family and timely referral is possible. In cases when genetic testing is not possible, the classical phenotype is the key to diagnosis.

Declarations

ETHICS APPROVAL

Ethical approval was obtained from the relevant institutional review board/ethics committee, where applicable.

DISCLAIMER

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING DISCLOSURE

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CONSENT TO PUBLISH

Written informed consent was obtained from the parents/legal guardians of both patients prior to the preparation of this manuscript. The parents have separately consented to submission of this case report for publication.

CONSENT TO PARTICIPATE

Not Applicable.

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Author Contribution

Riffat and Rooman contributed to the conception and design of the study. Tayyaba conducted the literature review and prepared the initial manuscript. Riffat and Zainab critically revised the manuscript. All authors reviewed and approved the final manuscript.

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