Case Report

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Severe Congenital Neutropaenia With ELANE Mutation: A Case Report

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Abstract

Congenital neutropaenia can be broadly divided into two subtypes: Severe congenital neutropenia (SCN) and cyclical neutropaenia. SCN is a rare genetically heterogeneous disease. This three-month-old baby girl presented with prolonged febrile illness and found chronic severe neutropenia. Cyclical neutropaenia was excluded by doing serial full blood counts. Bone marrow examination revealed reversal of erythroid to myeloid ratio with suppressed granulopoiesis. Here we report a genetically diagnosed infant with SCN due to ELANE mutation in Sri Lanka using clinical exome sequencing and we highlight the usefulness of giving priority to the analysis of ELANE mutations in a resource poor setting, as they are the most common group of mutations among all genetic mutations that result in congenital neutropaenia.

Keywords: Severe congenital neutropaenia, cyclical neutropaenia, ELANE mutation, granulocytic colony stimulation factor.

INTRODUCTION

Absolute neutrophil count (ANC) below $1.5 \times 10^9/l$ in the peripheral blood is defined as neutropaenia [1]. Severe congenital neutropaenia (SCN) is a rare genetically heterogeneous disease with an estimated incidence of 3-8.5 cases per million population [2]. We report an infant genetically diagnosed with SCN due to ELANE mutation which will help to expand the knowledge on clinical presentation, diagnosis and management on SCN.

CASE REPORT

A three-month-old baby girl, third-born child to healthy nonconsanguineous parents presented with prolonged febrile illness and was found to have persistent severe neutropenia. She had an uncomplicated antenatal and perinatal period.

Umbilical discharge was noted from day seven of life and there was delayed separation of the umbilical stump. During the hospital stay, she developed skin abscesses which were progressive. There was no family history of immunodeficiency or malignancy. She was adequately grown without dysmorphism. There was no lymphadenopathy or organomegaly. Her full blood counts were suggestive of persistent severe neutropaenia with normal other two cell lines. Cyclical neutropaenia was excluded by doing serial full blood counts. Bone marrow examination revealed reversal of erythroid to myeloid ratio, suppressed granulopoiesis, prominent lymphocyte, and monocyte precursors and there was no evidence of malignancy. Blood and urine cultures were negative. Significant growth of *Pseudomonas* species was detected in wound swab cultures and bone marrow cultures. Serology testing for viral infections was negative. Her immunoglobulin levels were within normal limits. Severe congenital neutropenia was genetically

diagnosed by identifying ELANE mutation on exon 4 with the variant of c.253G>A (p.Gly85Arg) using clinical exome sequencing. She was treated with broad-spectrum antibiotics and started on low dose granulocytic colony stimulation factor (G-CSF) (5µg/kg/day) daily. Even with higher doses of G-CSF, she showed minimal improvement in ANC. So, regular G-CSF was discontinued. She often suffered from recurrent skin abscesses and bacterial sepsis during follow up which required prolonged courses of intravenous broad-spectrum antibiotics and G-CSF.

DISCUSSION

Absolute neutrophil count in peripheral blood $< 0.5 \times 10^9/L$ is defined as severe neutropenia [1,2]. It is considered as chronic when neutropaenia is persistent for more than three months [1]. Congenital neutropaenia can be broadly divided into two subtypes: SCN or cyclical neutropaenia [3]. We have excluded cyclical neutropaenia in our patient by doing serial full blood counts.

ELANE mutations are the most recognized cause of congenital neutropaenia and account for 40%-55% of cases [3]. ELANE encodes a cytotoxic serine protease called neutrophil elastase and more than 200 ELANE mutations have been identified [2]. Congenital neutropaenia with ELANE mutations generally are not associated with extra-haematopoietic disorders but associate with more serious infectious complications [1,3].

SCN is characterized by impaired differentiation of myeloid cells with bone marrow evidence of maturation arrest of neutrophils at the level of promyelocytes [2]. Bone marrow examination is not always required to establish the diagnosis, but it is important to rule out malignancy. Individuals SCN usually present during the first six months of life [3]. They are prone to develop bacterial infections such as otitis media, gingivitis, pneumonia, superficial or deep abscesses and septicaemia from the neonatal period [2]. Compared to SCN, cyclical neutropaenia is less severe and the majority diagnosed after infancy [3].

SCN could be inherited autosomal dominantly or autosomal recessively. Autosomal dominant (AD) SCN is more common than autosomal recessive (AR) SCN. Targeted next-generation sequencing and exome sequencing is widely used as the diagnostic tool. The majority of individuals with AD SCN carry heterozygous ELANE

mutations whereas homozygous mutations in HAX1 had been identified with AR SCN[2].

The genetic diagnosis is always beneficial to rule out the differential diagnosis and plan specific management. The mainstay of therapy is daily subcutaneous G-CSF and vigorous treatment of infections [2,3]. The goal is to maintain ANC $> 1 \times 10^9/L$. It is recommended to start with a low dose of G-CSF (1-3 microgram/kg/day). If the patient is not responding the dose can be increased. Majority respond well to G-CSF. Overall survival of individuals with SCN is estimated to exceed 80% [2]. Approximately five percent of patients do not respond even to higher doses of G-CSF. Haemopoietic stem cell transplantation should be considered in patients with refractory disease [2,3]. The survivors of SCN need close follow up for haematological malignancies, most commonly acute myeloid leukaemia and myelodysplastic syndrome as SCN has its own risk of leukaemic transformation. Higher doses of G-CSF ($> 15 \mu g/kg/day$) can significantly contribute to haematological malignancies [2].

CONCLUSION

SCN is one subtype of congenital neutropaenia. Analysis for ELANE mutations should be given the priority in exome sequencing in a resource poor setting, as they are the most common group of mutations among all genetic mutations that result in congenital neutropaenia.

Author declarations

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Author contributions

TS was the major contributor in writing the manuscript. NH CU, and NT contributed to drafting the work and writing the manuscript. NS, CT, and KW were involved in writing, supervising, and editing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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Ethics approval and consent to participate

Consent for publication was obtained from parents.

Competing interests

The authors declare that they have no conflict of interest.

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