PAGNY RESEARCH DAY

Physician Affiliate Group of New York, P.C.

A Rare Autosomal Dominant CLPB (Caseinolytic Peptidase B) Mutation in a Newborn Presenting with Severe Congenital Neutropenia and Required Allogenic Bone Marrow Transplant

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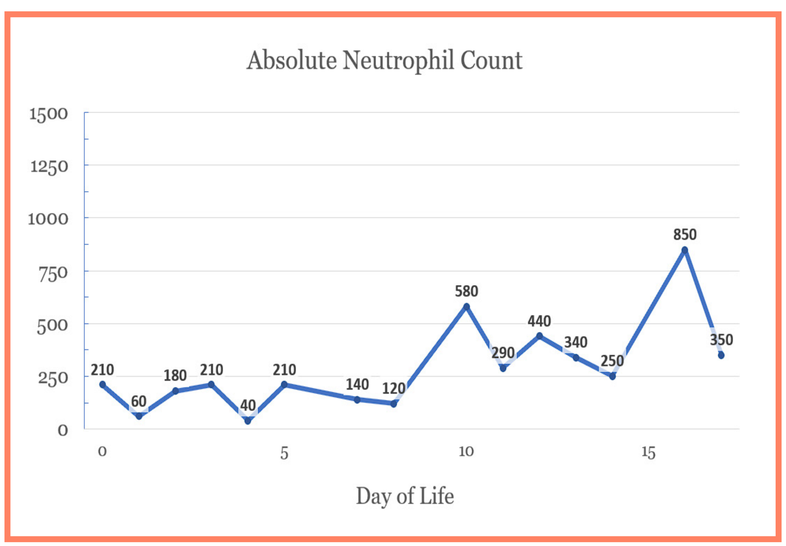
INTRODUCTION

Pathogenic CLPB mutation is an extremely rare condition of congenital neutropenia. We report a neonate who presented with respiratory distress following resuscitative delivery and severe neutropenia, not responsive to G-CSF (granulocyte colony-stimulating factor) treatment and required bone marrow transplantation.

CASE DESCRIPTION

A male born to non-consanguineous parents at 39 weeks via C-section due to Category II fetal tracing. Pregnancy was complicated by morbid obesity, gestational diabetes, severe preeclampsia with transaminitis. Delivery was further complicated by occult cord prolapse, nuchal cord; and newborn required resuscitation with PPV followed by CPAP. Apgars were 5 and 8 (at 1 and 5 min). Baby was admitted to the NICU with respiratory distress requiring CPAP support.

Initial blood gas results showed metabolic acidosis (pH 7.3, Bicarb 13.3 and BE-13), with consistent findings on umbilical cord gases. It responded to normal saline bolus (7.4/-6). The WBC count was 6.26, ANC 0, and CRP 56. The baby received a course of ampicillin and gentamicin for presumed neonatal sepsis. Blood cultures and CSF studies returned negative, and the CRP level normalized, but neutrophil counts remained low with normal T cell subsets.



CASE DESCRIPTION CONT.

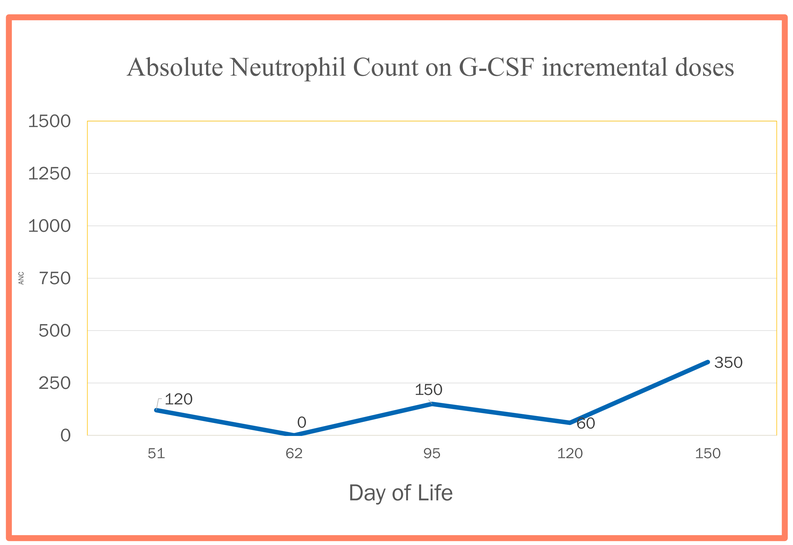
Initially thought of neutropenia secondary to maternal preeclampsia, or birth asphyxia but it failed to recover in due course of time.

Further work up was done for organic acidemias and neonatal alloimmune neutropenia and results were negative.

And this led to genetic factor as a possible cause of neutropenia.
Neutropenia genetic panel were sent on the newborn and both the parents which revealed a pathogenic CLPB mutation (c.1681C>T, p.Arg561Trp) on the newborn, whereas, both parents tested negative for the mutation. The finding was consistent with the diagnosis of autosomal dominant CLPB deficiency.

Patient received G-CSF but failed to respond to incremental doses.

Patient underwent allogenic bone marrow transplantation at 8 months; post-transplantation course was complicated by skin GVHD which was managed with tacrolimus. Patient is now 18 months and is growing well.



DISCUSSION

Severe congenital neutropenia has a prevalence of 5 cases per 1 million individuals. It is characterized by neutropenia related severe recurrent infections and, often associated with mild to severe syndromic features. Commonly associated genotypes are ELANE and HAX1.
Heterozygous autosomal dominant de novo mutations of CLPB is an extremely rare condition and incidence data is not available. To date 16 cases of de novo CLPB mutations have been reported.

Case reports on CLPB mutations

Nucleotide Change (cDNA)	Protein Change	Number of Cases
c.1163C>A	p.Thr388Lys (T388K)	1
c.1211A>C	p.Lys404Thr	1
c.1280C>T	p.Pro427Leu	1
c.1488T>A	p.Asn496Lys (N496K)	1
c.1669G>A	p.Glu557Lys (E557K)	1
c.1678G>A	p.Gly560Arg	2
c.1681C>G	p.Arg561Gly (R561G)	1
c.1681C>T*	p.Arg561Trp	2
c.1682G>A	p.Arg561Gln (R561Q)	4
c.1858C>T	p.Arg620Cys (R620C)	2

CLPB encodes an adenosine triphosphatase involved in protein folding and mitochondrial function. The mechanisms by which CLPB mutations impair granulocytic differentiation remains unclear. Some of these patients exhibit 3-methylglutaconic acid deficiency, neurological involvement (such as brain atrophy and myelination deficits), developmental delays, and cataracts.

CONCLUSION

CLPB mutation is an extremely rare cause of severe congenital neutropenia. We report an infant with de novo CLPB mutation who presented with severe neutropenia and required allogenic bone marrow transplantation.

REFERENCES

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