Am J Transl Res 2025;17(2):1153-1161
www.ajtr.org /ISSN:1943-8141/AJTR0159220

Case Report

Cyclic neutropenia: a case report and literature review

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Received July 15, 2024; Accepted January 13, 2025; Epub February 15, 2025; Published February 28, 2025

Abstract: To enhance the understanding of cyclic neutropenia (CyN) and improve the diagnosis and treatment of related diseases. Clinical data were analyzed from a 19-month-old child with recurrent infections and oral ulcers who was admitted to Inner Mongolia Maternal and Child Health Hospital on August 27, 2021 and a literature review was conducted. The patient developed an infection every 14-47 days, with fever, oral ulcers, bacterial infections, and decreased blood neutrophil counts at disease onset. There was no obvious abnormality in the bone marrow morphology, and genetic testing revealed heterozygous mutations in Neutrophil elastase (ELANE), leading to the diagnosis of CyN. For patients with periodic changes in clinical manifestations accompanied by granulocyte deficiency, bone marrow puncture and genetic testing of genes related to granulocyte deficiency should be performed. In patients with neutropenia, genetic testing can aid in the diagnosis of CyN.

Keywords: Congenital neutropenia, cyclic neutropenia, severe congenital neutropenia, ELANE, G-CSF

Introduction

Neutropenia is defined as a routine blood neutrophil count less than 1.5×10^9/L. Neutropenia can be divided into congenital and acquired neutropenia. Congenital neutropenia (CN) is a rare disease with an incidence of approximately 0.6/100,000 per year [1]. This subtype includes Kostmann syndrome, severe congenital neutropenia (SCN), cyclic neutropenia (CyN), and Schwachman-Diamond syndrome. Acquired neutropenia is caused by infections, drugs, nutritional deficiencies, and immune-related diseases. Patients with periodic neutropenia exhibit periodic episodes of neutropenia accompanied by fever and infection, often accompanied by oral ulcers during fever, at intervals ranging from 15 to 35 days. Typically, reported cycles range from 19 to 21 days, with neutropenia occurring continuously for at least 3 to 5 days per cycle. Neutrophil levels can return to normal on their own, and patients in the recovery phase may be asymptomatic. To date, the genes related to periodic neutropenia have been reported include ELANE, CSF3R, HAX1, WAS, and G6PC3. However, the most common pathogenic gene is the ELANE gene located on chromosome 19. We report a case of a patient with CyN in our hospital, describe their clinical data and laboratory test results, and review the literature on ELANE and CyN to further enhance our understanding of this disease and improve its diagnosis and treatment.

Patient information

The patient, a 19-month-old male, was hospitalized in our department beginning on August 27, 2021, due to oral ulcers lasting more than 10 days and fever lasting 4 days. Ten days prior to admission the patient developed oral ulcers. Four days prior to admission, the patient developed a fever with a maximum body temperature of 39.4°C and a fever peak occurring 3 times per day. Oral antipyretic medication could return the temperature to normal levels. The patient's family sought medical attention at a local clinic and was treated with topical and local oral medication for 3 days, but the effect was poor. The patient presented for medical attention at our outpatient department, and a complete routine blood test revealed a lack of granulocytes. To achieve systematic diagnosis and treatment, the outpatient department admitted the patient to the hospital with "granulocyte deficiency and herpetic stomatitis". The patient was hospital-

https://doi.org/10.62347/OLFS3168

ized for 11 days starting on April 13, 2020, due to external otitis media, suppurative otitis media, and granulocyte deficiency. The culture of the ear canal exudate tested positive for both Staphylococcus aureus and Streptococcus pneumoniae. Following 11 days of anti-infective therapy using ceftriaxone sodium, the patient exhibited significant improvement and was subsequently discharged. On May 17, 2021, he was hospitalized for 13 days due to infectious mononucleosis, neutropenia, moderate anemia, bronchopneumonia, mycoplasma infection, grade II laryngeal obstruction, acute laryngitis, and adenoid hypertrophy. Upon admission, the patient's neutrophil count was recorded at 0.01×10^9/L. The individual received a 13-day course of ceftriaxone sodium, an 8-day regimen of ganciclovir, a 6-day course of oral azithromycin, and a 4-day treatment with intravenous human immunoglobulin at a dosage of 5 g per day. Prior to discharge, a follow-up neutrophil count was conducted, which indicated an increase to 0.04×10^9/L. Subsequently, the patient was referred to Beijing Children's Hospital, where bone marrow morphology and immunophenotyping examinations revealed no abnormalities. On June 15, 2021, he was hospitalized for 8 days at a hospital in the Inner Mongolia Autonomous Region due to upper respiratory tract infection, mild anemia, and neutropenia. Throughout the period, the morphology of the bone marrow exhibited a reduction in the proportion of granulocytes, with cells at all stages below the myelocyte level being visible. These were predominantly composed of band neutrophils, and no abnormal morphological features were noted. After receiving symptomatic anti-infection treatment, the patient improved and was discharged from the hospital. On July 2, 2021, he was hospitalized in our hospital for 14 days because of "granulocyte deficiency, sepsis, and upper respiratory tract infection". Throughout the specified period, cefoperazone and sulbactam sodium were administered intravenously as part of the anti-infection therapy to maintain normal body temperature. Additionally, intravenous human immunoglobulin was administered to bolster the immune system. Subcutaneous injections of Granulocyte Colony Stimulating Factor (GCSF) were also given over a span of 6 days to stimulate the production of granulocytes. On July 29, 2021, he was hospitalized in our hospital for 7 days due to herpetic stomatitis virus disease and granulocyte deficiency, and received antiviral treatment with acyclovir for a duration of 7 days. Patient compliance was poor, and there was no regular follow-up after each discharge.

Personal history

The patient is G1P1, born at 38 weeks by cesarean section with a birth weight of 3900 g and was breastfeed. The patient was not vaccinated after 6 months. His physical development was lower than that of his peers. There was no history of allergies, trauma, or contact with animals such as cats or dogs. There was no contact history of tuberculosis, hepatitis B, or hand, foot and mouth disease, and there was no contact history of COVID-19 or pestis. The patient's parents had no history of recurrent granulocyte deficiency.

Admission examination

The patient's vital signs were stable, and his physical development was lower than that of children of the same age. His mental state was poor, and his consciousness was clear. There was no rash on the skin or mucous membranes of the whole body and no bleeding points, and there were many swollen lymph nodes in the neck, jaw, and groin, which were hard and had good mobility. There was no double eyelid swelling, lip redness, pharyngeal congestion, gingival redness or swelling. Several 2 cm*2 cm ulcerative surfaces were observed on the tongue tip and gingiva. Bilateral tonsils I were enlarged and congested, and no purulent secretions were observed. Regular, coarse breathing sounds in both lungs and no dry or wet rales were heard. No abnormalities were detected in the abdomen (the oral ulcers and perianal abscesses of this child are shown in **Figure 1A-C**).

Auxiliary examinations

No significant abnormalities in liver function, kidney function, myocardial enzymes, ions, blood coagulation, infection, or routine urine or stool tests were found. The pathogen examination results were as follows: Herpes simplex virus type I nucleic acid, 3242 copies/ml, significantly elevated; Brucella: negative; and urine and fecal cultures: all negative. The immune-related IgA, IgG, and IgM levels did not decrease; no abnormalities were detected in complement C3 or C4; and no abnormalities were

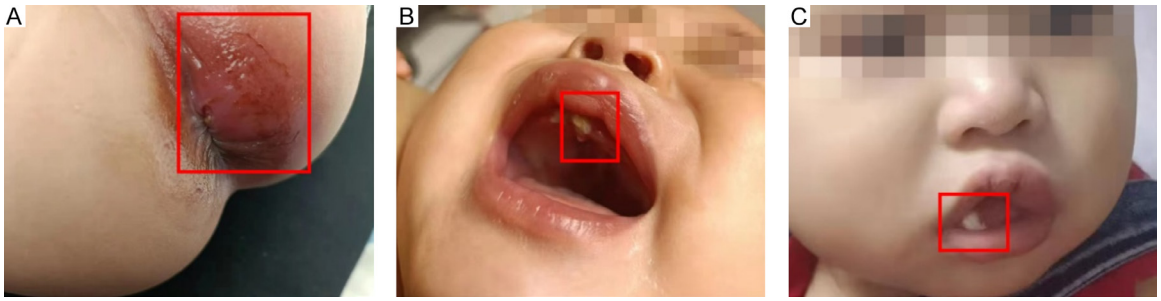

Figure 1. Perianal abscesses (A), Oral ulcers (B) and Ulcer on the surface of the tongue (C) in the patient.

Table 1. Routine blood test results during the first hospitalization

Date	WBC×10^9/L	HB g/L	PLT×10^9/L	NEUT×10^9/L	NEUT%	LYM%	CRP ng/ml
2020.4.13	10.68	110	458	0.55	5.1%	53.5%	-
2020.4.16	9.17	114	488	0.08	0.8%	71.6%	-
2020.4.20	6.51	114	463	0.04	0.5%	71%	-

Notes: WBC, white blood cell; HB, hemoglobin; PLT, platelet count; NEUT, neutrophil; NEUT%, neutrophil percentage; LYM%, lymphocyte percentage; CRP, C-reactive protein.

Table 2. Routine blood test results during the second hospitalization

Date	WBC×10^9/L	HB g/L	PLT×10^9/L	NEUT×10^9/L	NEUT%	LYM%	CRP ng/ml
2021.5.16	6.06	103	320	0.01	0.1%	51%	135
2021.5.17	8.12	104	368	0.04	0.5%	59.1%	-
2021.5.20	9.12	105	666	0.05	0.6%	71.5%	-
2021.5.24	4.36	98	640	0.04	0.8%	76.4%	-

Notes: WBC, white blood cell; HB, hemoglobin; PLT, platelet count; NEUT, neutrophil; NEUT%, neutrophil percentage; LYM%, lymphocyte percentage; CRP, C-reactive protein.

Table 3. Routine blood test results during the third hospitalization

Date	WBC×10^9/L	HB g/L	PLT×10^9/L	NEUT×10^9/L	NEUT%	LYM%	CRP ng/ml
2021.7.2	7.55	111	424	0.03	0.3%	37.1%	77.94
2021.7.6	6.81	86	352	0.06	0.9%	41.7%	-
2021.7.9	5.14	88	500	0.05	1%	47.5%	111
2021.7.13	12.18	115	745	0.6	5%	51.5%	19
2021.7.16	7.72	95	677	0.34	4.4%	74%	2.59

Notes: WBC, white blood cell; HB, hemoglobin; PLT, platelet count; NEUT, neutrophil; NEUT%, neutrophil percentage; LYM%, lymphocyte percentage; CRP, C-reactive protein.

Table 4. Routine blood test results during the fourth hospitalization

Date	WBC×10^9/L	HB g/L	PLT×10^9/L	NEUT×10^9/L	NEUT%	LYM%	CRP ng/ml
2021.7.30	5.57	107	354	0.07	1.3%	49.7%	32.29
2021.8.4	6.47	113	449	0.09	1.3%	64.5%	3.26

Notes: WBC, white blood cell; HB, hemoglobin; PLT, platelet count; NEUT, neutrophil; NEUT%, neutrophil percentage; LYM%, lymphocyte percentage; CRP, C-reactive protein.

detected in the levels of anti-nuclear antibodies. The echocardiogram revealed no abnormalities. Chest X-ray revealed no abnormalities. The routine blood test results of the patient during each hospitalization are shown in **Tables 1**-**5** and **Figure 2**. Genetic testing

Table 5. Routine blood test results during the fifth hospitalization

Date	WBC×10^9/L	HB g/L	PLT×10^9/L	NEUT×10^9/L	NEUT%	LYM%	CRP ng/ml
2021.8.27	6.65	113	449	0.05	0.8%	58.6%	124
2021.8.31	6.41	108	647	0.02	0.3%	68.2%	13.87
2021.9.5	6.22	109	544	0.11	1.8%	73.8%	<0.5
2021.9.9	8.02	108	587	0.03	0.4%	69.8%	2.27
2021.9.12	7.36	98	366	0.06	0.8%	52.4%	56.73
2021.9.16	8.55	104	383	0.27	3.2%	54%	9.67
2021.9.19	9.33	112	356	1.49	16%	54.2%	<0.5
2021.9.21	8.69	111	337	1.76	20.2%	49.5%	-

Note: WBC, white blood cell; HB, hemoglobin; PLT, platelet count; NEUT, neutrophil; NEUT%, neutrophil percentage; LYM%, lymphocyte percentage; CRP, C-reactive protein.

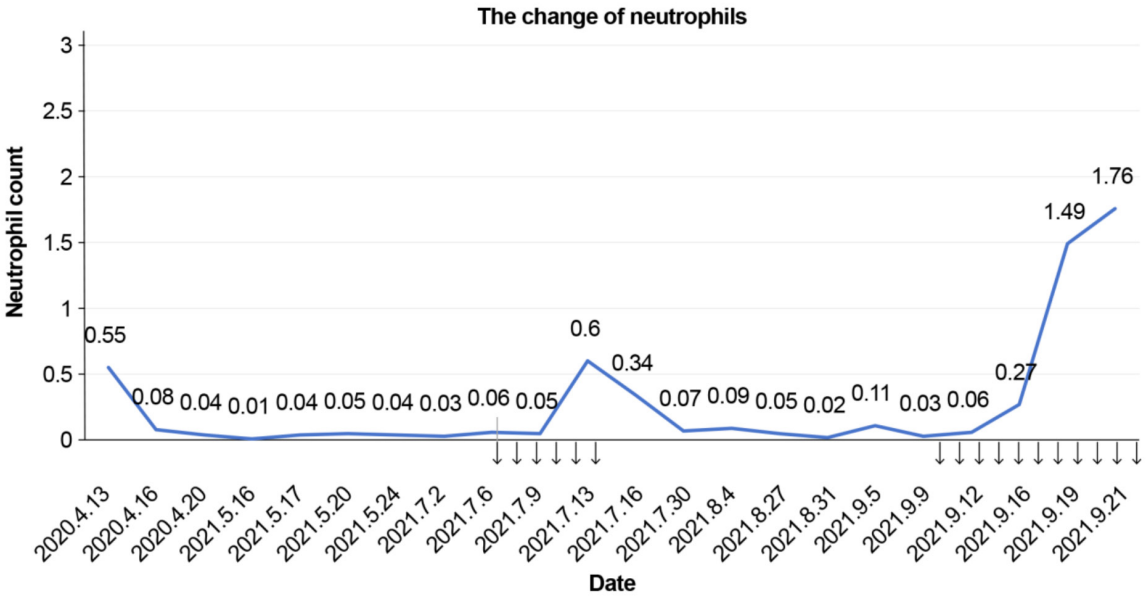

Figure 2. Downward arrows indicate subcutaneous injection of G-CSF; the unit for neutrophil count is ×10^9/L.

revealed a spontaneous, heterozygous of the ELANE gene, c.125C>T (**Figure 3**), and neither of the patient's parents had this mutation at this site. In this missense mutation, the 125th nucleotide in exon 2 of the ELANE gene on chromosome 19 is mutated from cytosine C to thymine T, causing the 42nd amino acid to change from proline to leucine. Based on the predicted protein function, this mutation is predicted to be a harmful mutation. According to the ACMG guidelines, this mutation is pathogenic and located in a hotspot mutation region.

Treatment

After admission, treatment with anti-infection agents, immunoglobulin support, and granulocyte colony-stimulating factor alleviated the patient's clinical symptoms. After 2 weeks of hospitalization, fever, oral ulcers, and perianal rupture recurred. A routine blood test revealed a decrease in the neutrophil count to 0.03×10^9/L. After treatment with acyclovir, ceftazidime, and granulocyte colony-stimulating factor, the patient's condition improved again. Upon re-examination, the neutrophil count had increased to 1.76×10^9/L.

Discussion

Neutropenia is defined as a decrease in the number of neutrophils in the peripheral blood below the normal range. Children over 1 year old have a count of less than 1.5×10^9/L, whereas those under 1 year old have a count of less than 1.0×10^9/L [1]. Severe chronic neutropenia

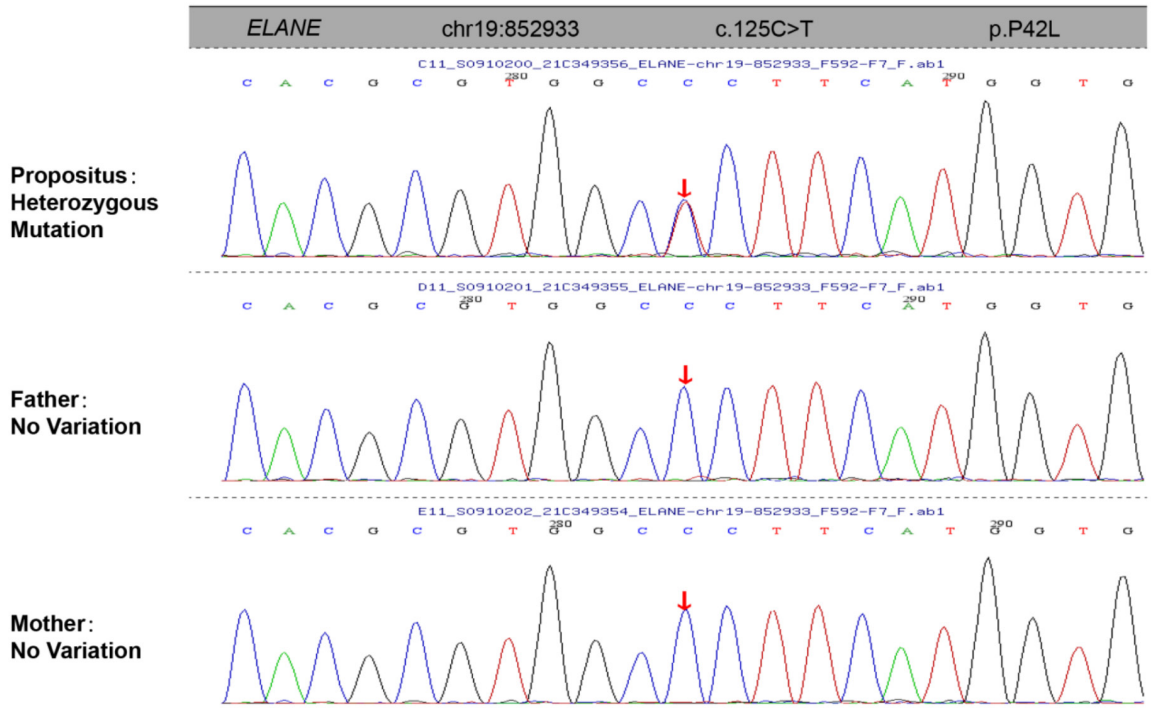

Figure 3. ELANE sequencing results: the 125th nucleotide of ELANE in the patient changed from C to T, indicating a spontaneous mutation.

includes severe congenital neutropenia (SCN) and periodic neutropenia (CyN) [2]. SCN is characterized mainly by severe neutropenia accompanied by recurrent and nonperiodic infections, which are usually severe and responds poorly to GCS-F; in contrast, CyN is characterized by a periodic reduction in granulocytes and has a better response to GCS-F. Congenital neutropenia (CN) is a group of syndromes of neutropenia in peripheral blood caused by gene mutation, which was first reported by Kostmann [3]. CN is a rare disease, with an extremely low incidence of approximately 6.2/1,000,000 [4]. Cyclic neutropenia is an autosomal dominant genetic disease in which the number of neutrophils in the peripheral blood decreases periodically, usually every 21 days. During the neutropenia phase, affected individuals are at risk of opportunistic infections. Monocytes, platelets, lymphocytes, and reticulocytes also circulate at the same frequency. In this patient, the lowest neutrophil count was 0.01×10^9/L, with intervals ranging from 15 to 31 days [5]. The possibility that both SCN and CyN may occur simultaneously cannot be ruled out. For patients with congenital neutropenia with ELANE mutations, if the cycle of neutropenia is not approximately 21 days, the patient may have both SCN and CyN, which is the innovation of this study.

A study revealed that congenital neutropenia is associated with at least 15 gene mutations, including ELANE, HAX1, G6PC3, VPS45, GFI1, JAGN1, and GSF3R [6]. Among them, ELANE is the most common gene that causes SCN and CyN, accounting for 50%-60% of cases, and has autosomal dominant or recessive inheritance [7]. This study reports a case of congenital neutropenia caused by ELANE mutation. In a screening study of ELANE, HAX1, and GFI1 gene mutations in children with neutropenia, a total of 60 children who experienced at least 3 or more instances of neutropenia within 3 months were included as the study subjects. Only 4 of them had gene mutations; all mutations were in the ELANE gene, and 2 of them were novel mutations [8], indicating a higher mutation rate of ELANE in patients with congenital neutropenia. This study used whole-genome screening and positional cloning to identify ELANE mutations located on chromosome 19p13.3 [5]. The patient in this case had heterozygous mutations in ELANE, including a missense mutation and a spontaneous mutation. The mutation is located on chromosome 19, which is consistent with the findings of Horwitz M et al. Nucleotide 125 changed from cytosine (C) to thymine (T), causing amino acid 42 to change from proline to leucine. According

to the comprehensive prediction of bioinformatics protein function by REVEL software, this mutation is predicted to be harmful.

The neutrophil elastase ELANE is a subfamily of serine proteases that hydrolyze many proteins in addition to elastin. Humans have six elastase genes that encode structurally similar proteins. The encoded protein undergoes protein hydrolysis to produce active proteases. After activation, this protease hydrolyzes proteins in specialized neutrophil lysosomes (known as azurophilic granules) and extracellular matrix proteins. This enzyme may play a role in degenerative and inflammatory diseases through the hydrolysis of collagen IV and elastin. This protein can also degrade outer membrane protein A (OmpA) of Escherichia coli, as well as the virulence factors of bacteria such as Shigella, Salmonella, and Yersinia. The mutation of this gene is associated with CyN and SCN. This gene is found in the gene cluster on chromosome 19. RNA-sequence was performed on tissue samples from 95 humans representing 27 different tissues, and this gene was expressed mainly in the bone marrow [9].

Autosomal dominant or sporadic mutations in ELANE are the most common cause of SCN, and the autosomal recessive inheritance of the HAX1 gene, encoding multifunctional proteins related to mitochondrial integrity and cytoskeletal tissue, can also lead to SCN, initially known as Kostmann syndrome [10]. It is not yet clear how mutations in ELANE, HAX1, and other genes that cause SCN affect the production of neutrophils. The common assumption is that the cellular stress in ELANE-SCN caused by neutrophil protein misfolding and that in HAX1-SCN caused by mitochondrial leakage are driving factors for neutropenia. A basic study on CyN revealed that the number of neutrophils in the peripheral blood circulation of CyN patients is slightly greater than that in SCN patients, and the clinical manifestations caused by neutropenia are not as severe as those in SCN patients. When the neutrophil count of the peripheral blood of CyN patients reaches its lowest value, the proportion of hematopoietic stem cells and hematopoietic progenitor cells in the bone marrow and the mRNA expression level of the ELANE gene increase [11]. These findings suggest that during the period of neutropenia in this patient, the severity of the condition may be evaluated by the proportions of hematopoietic stem cells and hematopoietic progenitor cells in the bone marrow. The Olofen PA research team demonstrated through RNA sequencing that the transcription of wild-type and mutant ELANE alleles is completely dependent on the presence of early myeloid leukemia protein. Early myeloid leukemia protein binds to the promoter/enhancer region of ELANE, regulating its transcription. In the bone marrow of patients with ELANE mutations, which cause misfolding of neutrophil elastase (NE) protein, CD34+CD45+ hematopoietic progenitor cells contain many early myeloid leukemia protein nucleosomes [12].

Malte U. et al. suggests that the ELANE gene does play an important role in neutrophil development [13]. ELANE contains 5 exons. All known ELANE chain-terminating mutations occur in the fifth and final exon which leads to SCN or CyN. The carboxyl-terminal portion of the polypeptide likely contributes functionally to prevent neutropenia [14]. In addition to being localized within neutrophil granules, neutrophil elastase is secreted and is found on the cell surface, as well as being detected within the nucleus [15]. There are studies speculating that mislocalization of mutant neutrophil elastase might contribute to disease pathogenesis based on several observations [16]. Further reports have additionally implicated ER stress and unfolded protein response in the emergence of SCN: accumulation of unfolded or misfolded neutrophil expressed (NE) proteins in the endoplasmic reticulum (ER) is believed to induce ER stress, resulting in induction of the unfolded protein response [17, 18]. Previous analyses indicate that NE mutations can lead to misfolding of the protein and subsequent induction of unfolded protein response (UPR) which then results in enhanced apoptosis. They find that start-site mutations, instead, force translation from downstream in-frame initiation codons, yielding amino-terminally truncated isoforms lacking ER-localizing (pre) and zymogen-maintaining (pro) sequences, yet retain essential catalytic residues. Some ELANE mutations, therefore, appear to cause neutropenia via the production of amino-terminally deleted NE isoforms rather than by altering the coding sequence of the full-length protein [19]. Utilizing a mini-gene splicing assay for ELANE intronic variants, Shu et al. identified a mutant ELANE allele leading to the creation of a premature termination codon [20]. Confocal microscopy re-

vealed heightened expression of myeloperoxidase and neutrophil elastase in the patient, suggesting a potential role for the unfolded protein response in the pathogenesis of the deep intron ELANE mutation.

A young man developed cyclic neutropenia as an adult and was found to have 2 cis de novo GFI1 mutations. Neutrophil elastase seemed mislocalized from the granules to the nucleus of his neutrophils. Moreover, he showed T-lymphocyte immunity to proteinase 3 and neutrophil elastase, and autoimmune destruction of his neutrophils was thought to be the cause of his cylic neutropenia [21]. Perihan Mir et al. found that mRNA expression levels of ELANE and unfolded protein response (UPR)-related genes (ATF6, BiP (HSPA5), CHOP (DDIT3), and PKR-like ER kinase (EIF2AK3)) were elevated, but antiapoptotic genes (Bcl-2 (BCL2) and bcl-xL (BCL2L1)) were reduced in CD34 cells tested at the neutrophils nadir. They suggest that in CyN patients, some Hematopoietic Stem and Progenitor Cells (HSPCs) escape the UPR-induced ER stress and proliferate in response to G-CSF to a certain threshold at which UPR again affects the majority of HSPCs. There is a cyclic balance between ER stress-induced apoptosis of HSPCs and compensatory G-CSF-stimulated HSPC proliferation followed by granulocytic [11]. There is a research team who developed 3 models: patient-derived induced pluripotent stem cells (iPSC), (human myeloid cell leukemia cells) HL60 cells transiently expressing mutant elastase, and HL60 cells with regulated expression of the mutant enzyme, and they have the characteristics of neutrophil differentiation and maturation disorder. The inhibitor is MK0339 (a cell permeable, orally absorbed inhibitor of NE), which also gives HL60 cells a higher potential to differentiate into mature neutrophils [22]. This is expected to become a treatment method for neutrophil developmental disorders. Dysregulation of transcription of ELANE and of transcription factors involved herein have been considered to be part of the pathogenesis [23, 24].

Compared with CyN patients, SCN patients have a significantly greater cumulative incidence of severe adverse events, including myelodysplasia, acute myeloid leukemia (AML), stem cell transplantation, and death. The risk of specific mutations such as G214R or C151Y evolving into AML is high [25]. Regular follow-up of the patient in this case was recommended, changes in routine blood and reticulocyte levels were monitored, and if necessary, bone marrow morphology was regularly monitored to identify abnormal hematopoiesis. In a study on neutropenia related to ELANE expression registered with the French Registry of Severe Chronic Neutropenia, SCN and CyN caused varying degrees of infection symptoms, with cellulitis (48%) and pneumonia (38%) being the most common severe infections. The most common pathogens are *Staphylococcus aureus* (37.4%), *Escherichia coli* (20%), and *Pseudomonas aeruginosa* (16%), with fungal infections accounting for 1% of all infections.

The patient in this study had a relatively high frequency of oral infections, as well as upper respiratory tract, throat, and lung infections. The patient had previously been infected with EB virus but had not yet developed a fungal infection. Severe neutropenia ($<0.2\times10^9$/L) and a high lymphocyte count ($>3.0\times10^9$/L) are associated with a high risk of infection. The risk of infection for patients is greater during infancy than for other age groups. The use of G-CSF treatment can reduce the incidence of oral infections and other infection events. In this case, the patient was treated with a subcutaneous injection of G-CSF in July 2021 and September 2021. Neutrophils began to increase significantly after 2-3 doses, which is consistent with the characteristics of a study in France. A daily dose of G-CSF greater than 10 μg/kg does not reduce the risk of infection. Thirty-three percent of patients have permanent consequences, with the most common being tooth decay [26].

In summary, congenital neutropenia is characterized mainly by varying degrees of recurrent infections. For periodic neutropenia, this infection occurs in periodic episodes. For severe congenital neutropenia, infection is often severe, and conventional anti-infection measures may be ineffective. G-CSF has a certain therapeutic effect. Genetic testing is the main diagnostic method.

The study's limitations include suboptimal patient compliance, inconsistent post-discharge follow-up, absence of regular granulocyte-stimulating factor therapy, and challenges in monitoring treatment outcomes. The child's case represents a spontaneous mutation, with only

the parents confirming the genetic alteration. No other family members have been diagnosed with the disease, and genetic testing has not been conducted on them.

Acknowledgements

The present study was supported by the Inner Mongolia Autonomous Region Health Commission Project (grant No. 202202095).

Disclosure of conflict of interest

None.

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