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CLINICAL CASE OF AUTOSOMAL DOMINANT CYCLIC NEUTROPENIA

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კლინიკური შემთხვევა: აუტოსომურ-დომინანტური ციკლური ნეიტროპენია

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რეზიუმე

ციკლური ნეიტროპენია არის ერთ-ერთი იშვიათი ჰემატოლოგიური დაავადება, რომელსაც ახასიათებს ეპიზოდური ნეიტროპენია. ეს ეპიზოდები ვლინება 21-29 დღეში ერთხელ და ამ პერიოდში პაციენტებს ახასიათებთ ინფექციური დაავადებები. ეს სტატია განიხილავს ციკლური ნეიტროპენიის ერთ კლინიკურ შემთხვევას, მის დიაგნოზს, ეპიდემიოლოგიასა და ამ დაავადების მართვაში მულტიდისციპლინარული გუნდის ჩართვის აუცილებლობას.

Case description: The patient is a 3-year-old girl with recurrent infections that started in infancy. The infection occurs about once every month, and treatment with antibiotics is required each time. The patient is the first child of healthy parents and has one healthy younger brother.

The past medical history of this patient is one episode of sepsis during infancy. One year ago, she also had severe pneumonia, which required hospitalization. The patient has a recurrent herpes-like rash in the oral cavity. She also had one episode of oral candidiasis, which was treated with fluconazole. The mother also mentions many episodes of urinary tract infection and acute otitis media. Recently, the patient had an abscess in the axillary region, and after one month, a similar abscess was developed on the finger. Both conditions required antibiotic therapy.

The one thing that caught our attention was that during every infection, there was a decreased number of neutrophils on complete blood count tests. Here is an example of CBC from one of the episodic infections:

Segmented neutrophils	12	25-60	%
	0.70	1.12-6.0	10^9/L
Eosinophils	19	0.5-7	%
	0.93	0.02-0.7	10^9/L
Monocytes	21	2-10	%
	1.23	0.09-1	10^9/L
Erythrocyte sedimentation rate (ESR)	27	4-12	mm/h

After these findings, additional tests were done:

Total Immunoglobulin E (IgE)	113	0-3 years: median- 6,4 3-16 years: median- 25 Adults: median- 43	IU/ml
IgA	1.12	0.8-2.2	g/l
IgM	1.18	0.55-2.2	g/l
IgG	24.9	6.5-18	g/l
Fasting Insulin Abbott ELISA	3.6	5.0-20	µIU/ml
CD8 percentage	8.77	13.3-41.5	%
Absolute CD8 count	267	291-1238	Cells/ µl
ANA-Antinuclear Antibody	Negative	Negative	

So, genetic testing was recommended, for both parents and the patient and the results were as follows: The result of the patient: A heterozygous likely pathogenic variant was identified in the ELANE gene, which is consistent with a genetic diagnosis of autosomal dominant neutropenia, severe congenital type 1. Both parent genetic tests showed no abnormalities, thus this mutation is considered a de novo mutation. The patient was recommended follow-ups with immunologists and pediatrics. The patient was also advised to get an annual flu-vaccinations. She was prescribed the granulocyte-colony stimulating factor agent-filgastrim. If there is no response to filgastrim treatment, then the patient will be the candidate for hematopoietic stem cell transplantation.

Discussion: Severe congenital neutropenia, or Kostmann syndrome, was initially described in 1956 as an autosomal recessive disorder characterized by severe neutropenia and recurrent bacterial infections. Kostmann reported neutropenia accompanied by a promyelocytic maturation arrest in the bone marrow in an inbred family from northern Sweden. Subsequently, severe congenital neutropenia is genetically heterogeneous, with most cases arising sporadically and clinically similar to those initially reported by Kostmann [1].

According to the newest information, several mutations are associated with severe congenital neutropenia. These are: Neutrophil elastase (*ELANE*), *CSF3R* (20%-30%), *WASp*, *HAX1*, and *GFI1* mutations. This suggests that errors in trafficking and the unfolded protein response (UPR) may trigger premature neutrophil cell death. From those mutations, the *ELANE* (previously *ELA2*) mutation accounts for about 50-60% of patients with severe congenital neutropenia. It is not yet entirely understood why the neutrophil elastase mutation, a serine protease made primarily at the promyelocytic stage of neutrophil production, can result in either cyclic neutropenia or severe congenital neutropenia. Some experts consider one hypothesis that neutrophil elastase mutations may disrupt intracellular trafficking. This, in turn, may lead to activation of the UPR and, ultimately, apoptosis of granulocytic precursors [2].

Epidemiological data are limited, given the overlapping case definitions of congenital neutropenia and few patient registries. According to International Neutropenia Registry data from 2003 covering areas with a population of 700 million in the United States, Canada, Australia, and Europe (excluding France), 731 cases were reported, with a prevalence of about 1 per million people. A French registry reported an incidence as high as 6 cases per million people. Of the patients from the French survey, 30% had *ELANE* mutations (20% with severe congenital neutropenia and 10% with cyclic neutropenia), 30% had Shwachman-Diamond syndrome (SBDS), 5% had glycogen storage disease type 1b, and 35% had other disorders (1 or 2% each). In another study from the North American Severe Chronic Neutropenia Tissue Repository, mutations in *ELANE* genes were found in 90 (55.6%) of 162 patients. Of 72 patients with normal *ELANE* genes, 45 had sufficient DNA to undergo throughput sequencing to determine the prevalence of other mutations (*HAX1*, *WASp*, *SBDS*, *GFI1*, and *G6PC3*). Five of these patients were found to have mutations: *G6PC3* in 2, *GFI1* in 1, *SBDS* in 1, and *WASp* in 1. In 40% of patients, a genetic etiology for severe congenital neutropenia was unknown [2]. Generally, neutropenia is classified as mild, which is less than 1500 granulocytes/μL; moderate- less than 1000/μL; severe- less than 500/μL, and very severe, is less than 200/μL [2].

Severe congenital neutropenia usually presents in infancy with an absolute neutrophil count of less than 200/μL (0.2×10^9/L). These patients, before the availability of myeloid growth factors, usually died from severe bacterial infections in early childhood [1]. In general, the mortality rate is about 70% within the first year of life in the absence of medical intervention with granulocyte colony-stimulating factor (G-CSF), bone marrow transplantation, or peripheral blood stem cell transplantation [2]. But as in the early 1990's, clinical trials demonstrated that patients' blood neutrophil counts could be increased and

the frequency of infections decreased with long-term treatment with recombinant granulocyte-colony stimulating factor (G-CSF) for the first time and this finding led to the identification of many more cases that were previously unrecognized and intensified investigations into possible disease mechanisms [1].

Neutropenic patients are usually infected by organisms of their endogenous flora of the mouth, oropharynx, gastrointestinal tract, and skin. The susceptibility to bacterial infections even in the presence of severe neutropenia varies considerably. On the other hand, gingivitis and mouth ulcerations are the most common problems initially encountered by patients with severe congenital neutropenia because of the role of neutrophils in protecting the oral mucosa from bacterial infusion. Thus, patients with severe congenital neutropenia usually present in the first year of life with stomatitis, gingivitis, perirectal inflammation, or cellulitis. Abscesses, pneumonia, and septicemia may also occur [1]. They are not initially predisposed to other fungal, parasitic, or viral infections, but have a higher risk of fungal infection with prolonged neutropenia or extended antibiotic use.

Laboratory Studies of severe congenital neutropenia commonly show monocytosis and eosinophilia. Total leukocyte counts are frequently normal because of the monocytosis. Mild anemia may be present from chronic inflammation, and thrombocytosis may be present. Quantitative immunoglobulins may show hypergammaglobulinemia. Patients have a normal response to vaccinations. Complement levels typically are normal. Anti-neutrophil antibodies are absent but should be checked to exclude an autoimmune etiology when the diagnosis is entertained in the first few months of life [2].

Treatment. Antimicrobial prophylaxis may be useful in preventing recurrent infections. Oral sulfamethoxazole/trimethoprim sulfate (Bactrim) as a once daily, 50 mg/kg/d dose has been used. This only partially prevents the gingivostomatitis associated with severe congenital neutropenia. Concurrent therapy with metronidazole, which covers oral saprophytic flora, especially anaerobes, also may be added.

Hematopoietic growth factors (granulocyte colony-stimulating factor [G-CSF] and granulocyte macrophage colony-stimulating factor [GM-CSF]) are used to correct neutropenia. G-CSF has been used since the late 1980s and has shown a greater than 90% response rate. G-CSF is more efficacious and tolerable than GM-CSF, with less flu-like syndrome and less marked eosinophilia. There are 2 forms of G-CSF available:

Pegfilgrastim (Neulasta). Pegfilgrastim is the pegylated, covalent conjugate of G-CSF, a combination of filgrastim and polyethylene glycol, with a half-life of 15-80 hours, which decreases the number of injections needed from daily to once weekly. In various case reports, Pegfilgrastim is clinically efficacious and improves compliance and quality of life. However, in an observational study of 17 patients from the French Severe Chronic Neutropenia Registry who received Pegfilgrastim, only half the patients prescribed were able to continue this medication long-term because of adverse events and lack of efficacy. Further studies evaluating long-term outcomes are required.

Filgrastim/lenograstim (G-CSF). There is an induction phase with G-CSF to evaluate the response of individuals, with an increase in absolute neutrophil count (ANC) (>1500/µL) and clinical improvement after 10-15 days. The initial daily dose is 5 µg/kg subcutaneously. If there is no response after 15 days, the daily dose is increased by 5 µg/kg. The dose is halved if the response is rapid or excessive (ANC >5000 /µL). Once the minimal daily dose is determined, the maintenance phase can begin, with monitoring of neutrophil counts every 3-6 months. Almost two-thirds of patients respond to a daily dose of 2-10 µg/kg, while 20% respond to 10-20 µg/kg. A small percentage of patients require higher doses, up to 100 µg/kg. Around 10% of patients are unresponsive to G-CSF therapy.

Consultation is recommended with a pediatric immunologist, hematologist, and dentist. Provide genetic counseling to parents of infants because Kostmann disease has an autosomal recessive form of

inheritance. Obtain a CBC count with differential twice per week during the first four weeks after the initiation of granulocyte-colony stimulating factor (G-CSF) or for two weeks following any dosage adjustments. After that, obtain a CBC count with differential monthly for six months. When the minimum daily dose is found, the maintenance phase can be started, with monitoring of absolute neutrophil counts every 3-6 months.

Routine clinical follow-up every three months is recommended. Maintaining an adequate absolute neutrophil count (≥1000/μL) with G-CSF is central to preventing infections. Annual bone marrow examination for morphology and cytogenetic testing should be performed to identify any changes indicating malignant transformation and allow for early intervention with bone marrow transplantation. Regular G-CSF receptor analysis should also be performed to identify mutations. Most complications relate to infections. Bone demineralization occurs in approximately 50% of patients, which may result in bone pain and unusual fractures, either as part of the disease's pathophysiology or potentially from either endogenous or exogenous G-CSFs by increased bone resorption.

About 1 in 5 patients with severe congenital neutropenia develop secondary malignancies. The incidence of acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) in severe congenital neutropenia after ten years of G-CSF treatment is 21%.

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SUMMARY

Cyclic neutropenia is a rare hematological disorder characterized by fluctuations in blood neutrophil counts, which lead to episodic neutropenia once every 21-29 days and those episodes are manifested by infections. This article presents a clinical case of cyclic neutropenia, reviews the evaluation, clinical management and epidemiology and the role of the multidisciplinary team in managing patients with this condition.

Keywords: cyclic neutropenia, clinical case