Severe Congenital Neutropenia in Iran

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J Clin Immunol 2007; In press.

BACKGROUND

Severe Congenital Neutropenia (SCN)
also known as Kostmann syndrome,
is a rare inherited disorder,

characterized by:
early onset recurrent infections
in association with persistent severe neutropenia

BACKGROUND

The SCN patients typically have persistent severe neutropenia of less than 0.5 $\times 10^9$/L,
increased susceptibility to recurrent severe bacterial infections from early infancy,
and early-stage (promyelocyte-myelocyte) maturation arrest of myeloid differentiation in the bone marrow

BACKGROUND

Rolf Kostmann first described severe congenital neutropenia as an autosomal recessive disorder in 1956.

Subsequently, autosomal dominant and sporadic forms of the disease have been recognized.

BACKGROUND

Candidate Genes:

* ELA2 Mutations (AD)

* HAX1 Mutations (AR)

BACKGROUND

In the absence of appropriate treatment, affected children suffer from early life threatening infections.

In addition most patients die due to these infections despite antibiotic treatment.

Administration of recombinant human granulocyte colony-stimulating factor (G-CSF) could normalize neutrophil numbers in these patients to improve the prognosis and their quality of life.

OBJECTIVE

In order to determine the clinical and laboratory findings of Iranian patients with SCN, the records of 18 patients, who had been referred to the referral immunology and hematology departments in Iran, were reviewed.

METHODS

These data have already been gathered by interviewing the patients and reviewing their medical documents during a 20-year period (1986-2006).

RESULTS

Characteristics of patients

* Eighteen SCN patients: 10 male and 8 female

* Mean age: 8.8 ± 5.8 years

* In 10 families, parents were consanguine (55.6%)

* A history of recurrent infections in siblings of the affected patients was found in 4 families

RESULTS

Characteristics of patients

* The first manifestation had occurred at a median age of 4 (range: 1-20) months.

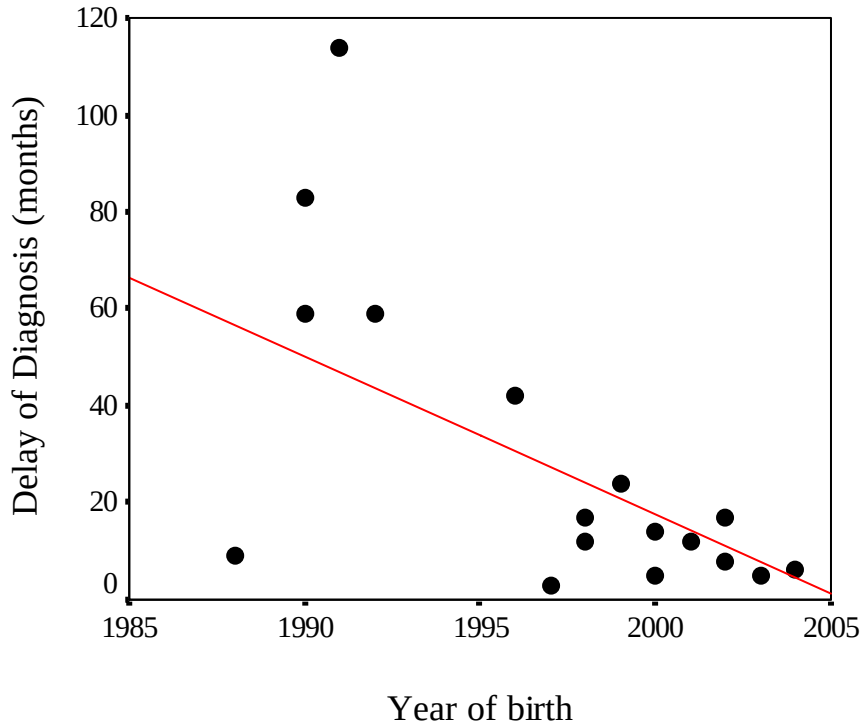
- Fifteen cases experienced symptoms by the age of 6 months

-Only 1 patient did not experience any symptoms until the age of 1 year

* The median age of patients at the time of diagnosis was 21 months (range: 5 months- 10 years),
with a median diagnosis delay of 15.5 months (range: 3 months- 9.5 years)

RESULTS

Characteristics of patients

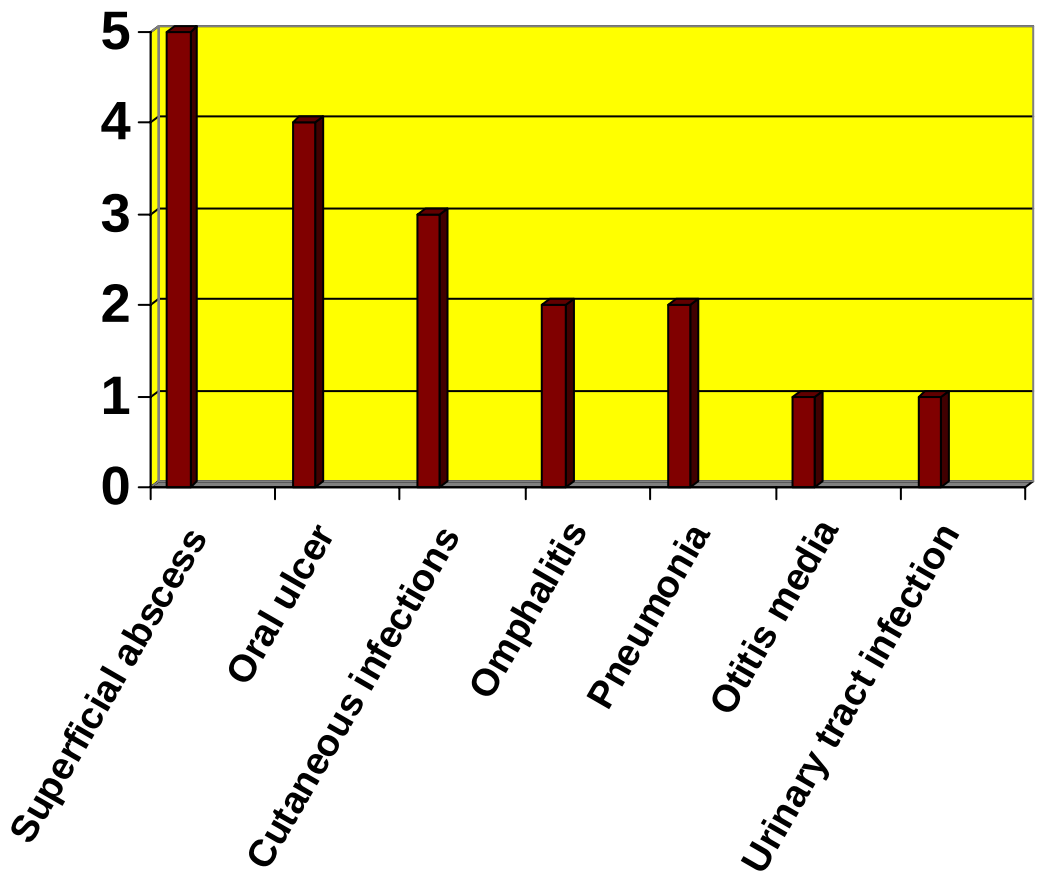


* The diagnosis has increasingly been made at an earlier age in more recent years
(r= -0.611, F= 9.554, P-value=0.007)

* A reverse association was observed between years of birth and delay of diagnosis

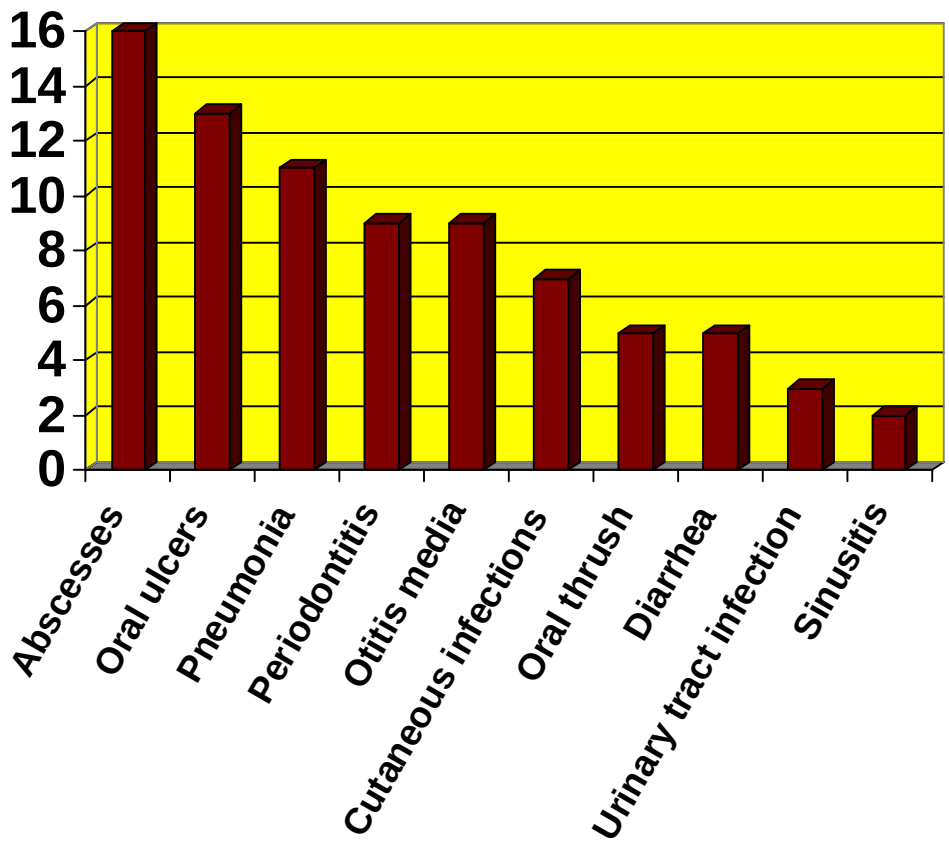
RESULTS

Presenting Manifestations



RESULTS

Clinical Manifestations



RESULTS

Clinical Manifestations

* During the course of disease, all patients developed mucocutaneous manifestations, and 16 cases had respiratory infections.

* Five patients had failure to thrive.

* Two patients had been complicated with bronchiectasis due to recurrent and severe pneumonia.

* Non-specific symptoms like hepatomegaly and splenomegaly were detected in 4 and 6 cases, respectively.

RESULTS

Clinical Manifestations

Abscesses have been detected as most frequent manifestations of patients, in different organs, including:

Cutaneous (10 cases)
Mastoidal (5 cases)
Perianal (3 cases)
Sacral (3 cases)
Dental (2 cases)
Submandibular (1 case)
Hepatic (1 case)

RESULTS

Hematological Studies

* All of these patients had already experienced severe neutropenia.

* ANC was low in these patients, with the mean count of 281.4±137.7 cells/mm^3

* Total white blood cell (WBC) counts ranged from normal to markedly elevated numbers in patients with acute infections.

* Six patients had anemia, six had thrombocytosis, and five patients had leukopenia; two had lymphocytosis, two had eosinophilia and one patient had monocytosis

RESULTS

Immunological Studies

* Laboratory analysis revealed an increased IgG serum level, with median of 1534.5 (range: 920-3800) mg/dl.

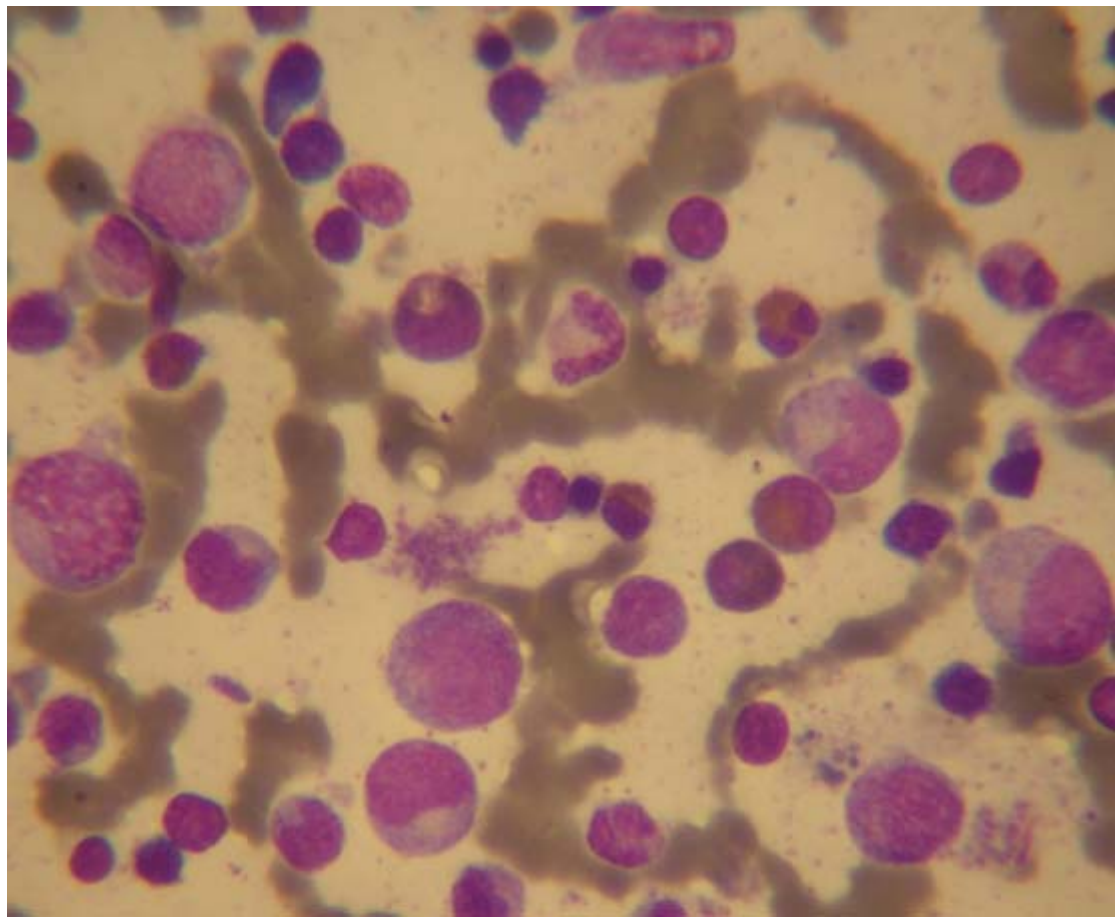
* The median serum levels for IgM and IgA was 126 (68-491) mg/dl and 85 mg/dl (30-730 mg/dl), respectively.

* 13 patients had higher serum level of IgG (72.2%), while 6 of these patients had also higher serum level of IgM and 5 had higher serum level of IgA as well

RESULTS

Bone Marrow Studies

Maturation arrest of neutrophil precursors at an early stage (promyelocyte-myelocyte)



RESULTS

Molecular Studies

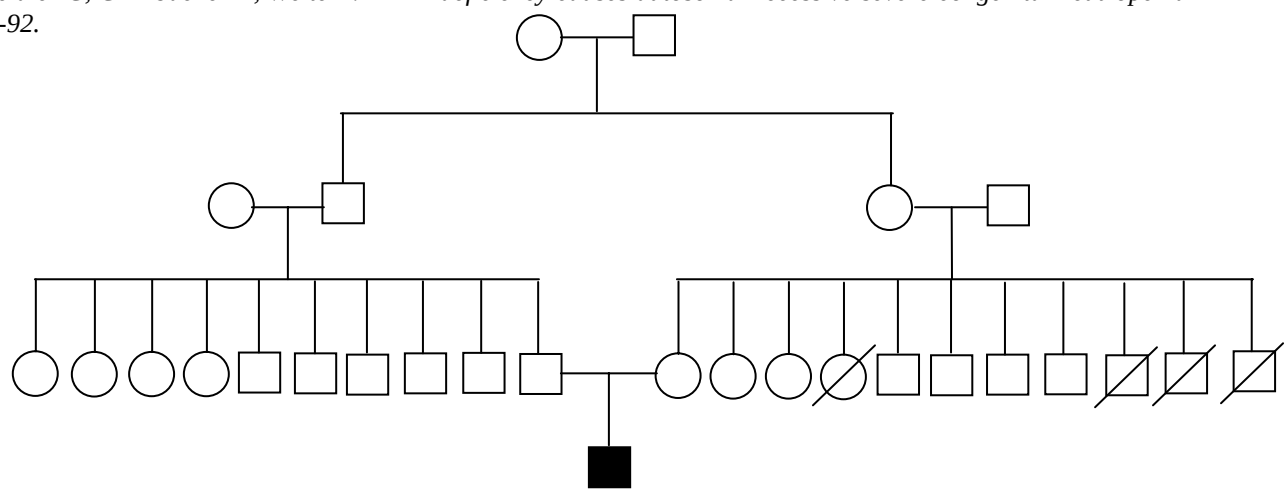
* Molecular analysis was conducted in 8 patients

* One patient had mutations in ELA2 gene

Salipante S, Benson KF, Luty J, Hadavi V, Kariminejad R, Kariminejad MH, Rezaei N, Horwitz MS. Double de novo mutations of ELA2 in cyclic and severe congenital neutropenia. Hum Mut 2007; In press.

* Three patients had mutations in HAX1 gene

Klein C, Grudzien M, Appaswamy G, Germeshausen M, Sandrock I, Schäffer AA, Rathinam C, Boztug K, Schwinzer B, Rezaei N, Bohn G, Melin M, Carlsson G, Fadeel B, Dahl N, Palmblad J, Henter JI, Zeidler C, Grimbacher B, Welte B. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). Nat Genet 2007; 39(1): 86-92.



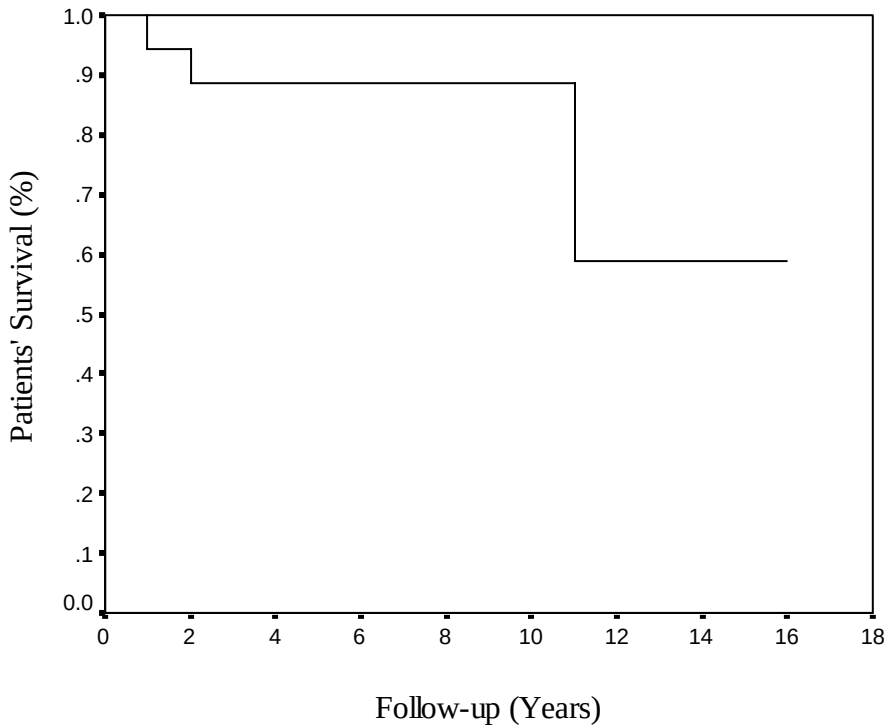
RESULTS

Mortality

* Twelve out of these patients are alive, 3 patients could not be localized, and the remaining 3 patients have already died, all due to septicemia

* Post-diagnosis survival was estimated as 90% for the first 2 years, which remains the same until 11 years after diagnosis when a drop of nearly 30% in survival

* None of our patients developed myelodysplastic syndromes or acute leukemia.



DISCUSSION

Although SCN is a rare disorder, the severe and recurrent infections should always raise a suspicion, which deserves further evaluation for detecting such disorder.

Genetic studies are useful nowadays in establishing the diagnosis and in differentiating the types of congenital neutropenias; however the diagnosis rests primarily on the clinical picture of the disorders and family studies, while these disorders share similar blood and bone marrow pictures.

DISCUSSION

Recurrent infections are the hallmark of severe neutropenia.

Common sites of infection include the oral cavity and mucous membranes, where mouth ulcers and periodontitis are common.

Examination of the oral cavity, perianal region, and skin is necessary in order to assess the clinical impact of neutropenia.

Recombinant human G-CSF is the first choice of treatment for SCN patients that could increase the number of neutrophils, reduce the number of infections and hospitalization, and improve the prognosis and their quality of life.

CONCLUSION

Severe and recurrent infections must always initiate the search for an immunodeficiency syndrome, because a delay in diagnosis may result in chronic infection, irretrievable end-organ damage or even death of the patient.

Timely referral to a hematologist and/or clinical immunologist remains the key to the successful diagnosis and management of patients with SCN

Thanks for your attention