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Congenital Neutropenia in Iran: Clinical- and Laboratory Evaluation, Treatment and Outcome in a Historical Cohort

Neutropenia is commonly observed in paediatric practice. Various states such as infection, auto-antibodies or chemotherapeutic treatment cause neutropenia. However, congenital neutropenia (CN) is one of the primary immunodeficiency diseases developed due to genetic alterations. Infectious symptoms are among the common manifestations. Mutations in HAX-1, G6PC3, jagunal and VPS45 for autosomal recessive, mutation in ELANE for autosomal dominant and mutation in WAS gene for X-linked version of CN were described. A substantial number of CNs remained unclassified and with unknown genetic disposition.

Methods: Patients registered in the Iranian Primary Immunodeficiency Registry (IPIDR), and referred to our clinic from 1997 until 2017 in the Children's Medical Center, were reviewed to identify cases with CN confirmed by at least 3 complete blood counts (CBC). The data were gathered from the medical records.

Results: From 87 cases in the registry, 37 patients were eligible including 21 males and 16 females with a mean age at time of inclusion of 5,08 ± 8,09 years. About half of the patients (19 out of 37 cases) had consanguineous parents and 27% (10 out of 37 cases) had at least one family member with a history of recurrent infections or confirmed immunodeficiency disease.

The most prevalent infectious symptoms among our patients were oral and teeth related complaints including inflamed gums, oral thrush or ulcers in 25, aphthous stomatitis in 18, and gingivitis in 12 cases. Respiratory infections in 21 cases and skin abscesses in 20 patients were developed. Cardiac malformations were observed in 4 cases. Facial dysmorphia, seizures and mental retardation and urethral reflux were also reported.

The mean of the first absolute neutrophil count (ANC) after referral was 310 ± 504 cells/mm3. To classify the patients, 19 cases had severe CN (ANC<500), and 18 cases had moderate CN (500≤ANC<1000). Bone marrow aspiration was performed in 26 cases, among which 17 cases had a maturation arrest in the myeloid series and 4 had a hypocellular status.

Genetic analysis showed HAX-1 mutation in 4 cases, and ELANE mutation in 4 cases. Whole exome sequencing revealed G6PC3 mutation in 1 and WHIM syndrome in 1 case and 27 patients remained genetically unclassified.

All patients received granulocyte-colony stimulating factor (G-CSF). Regular G-CSF for 17 cases, irregular G-CSF for 15 cases and PEGylated G-CSF for 5 cases were administered. The mean ANC was improved by the treatment (1895 ± 3775).

After the median of follow-up of 36 months from the time of diagnosis, cumulative mortality was 10% (n=4) after 2.5 years of observation. The cumulative survival (CS) was higher in children from not related parents compared with the cases with consanguineous parents (CS 0,92 CH 0,08 vs CS 0,78 CH 0,25 after 2 years). However, this was not significant (P = 0.07, Breslow test)

Discussion: Our study showed autosomal recessive CN is more common in countries with high rates of consanguinity like Iran. A few patients in our study were genetically classified. This might suggest that there are autosomal recessive genes causative of neutropenia that have not been described yet.