All of the following statements regarding severe congenital neutropenia are true, except:

1. X-linked neutropenia is related to the gain of function defect in WAS
2. Disseminated viral infections are commonly seen
3. Gingivitis and periodontitis are seen in patients with severe congenital neutropenia
4. Short stature and bone defect are seen in JAGN1 defect

Correct answer: 2

Explanation:
Severe congenital neutropenia is usually diagnosed during early childhood. In neonates, acute and severe umbilical infection is a diagnostic clue, which can occur within the first days of life. During the neonatal period, fevers associated with respiratory symptoms, including signs of pneumonia can also occur. Skin infections or deep tissue abscesses can also be the manifestations of congenital neutropenia. Severe gingivitis and periodontitis are often seen within the first 2 years of life. There are often long delays between the first symptoms and the confirmation of the diagnosis. Furthermore, neutropenia in early childhood is commonly an autoimmune disorder, which usually remits spontaneously over the first 3 or 4 years of life, so low absolute neutrophil counts (ANCs) are often dismissed as unconcerning.
Question 13

Early diagnosis of severe congenital neutropenia depends on an astute clinician recognizing that recurrent fevers and infections suggest an underlying haematological or immunological problem. Recurrent and painful mouth sores or teeth or gums problems are other important clues to prompt blood cell counts.

The pattern of inheritance can assist in confirming the diagnosis. For example, autosomal dominant mutations in *ELANE* are the most common cause of cyclic neutropenia and severe congenital neutropenia. Mutations in *ELANE* should be suspected and might be recognized in the first months of life if a child is ill and a family member already has the diagnosis of severe congenital neutropenia associated with *ELANE* mutations. Conversely, patients affected by diseases that are inherited in a recessive manner, for example, severe congenital neutropenia due to mutations in *HAX1*, *G6PC3*, *JAGN1* or *SBDS*, among others, are usually the first member of their family to receive the diagnosis of severe congenital neutropenia. Severe congenital neutropenias associated with mutations in *TAZ* (which cause Barth syndrome) or *WAS* have X-linked inheritance.

When there are no congenital organ anomalies or other clinical clues, the standard approach for children who present with severe neutropenia and whose bone marrow examination shows maturation arrest is sequencing candidate genes that have been associated with severe congenital neutropenia. It is reasonable to sequence *ELANE* first, as it is the most common mutation. As *ELANE* mutations can cause severe congenital neutropenia or cyclic neutropenia, sequential blood counts at regular intervals, possibly every day or every other day, are needed to make the diagnosis of cyclic neutropenia with greatest confidence.
If a heterozygous mutation in \textit{ELANE} is found, most clinicians do not recommend further genetic testing. If \textit{ELANE} sequencing is negative, other individual genes could be analysed, on the basis of family history and available resources. In consanguineous families, the search for autosomal recessive mutations would be recommended (starting with \textit{HAX1}). If these tests are also negative, sequencing of a panel of neutropenia-associated genes or whole-exome sequencing would be recommended. The panel sequencing approach is being used increasingly as a first choice and could be ultimately less expensive and more informative, as it can also uncover multi-gene mutations.

**Reference and suggested reading:**