

Cancer Prone Disease Section

Mini Review

Shwachman-Diamond syndrome (SDS)

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Identity

Inheritance

Autosomal recessive inheritance. Male to female ratio 1.7 : 1.

Clinics

Note

Bone marrow failure syndrome with exocrine pancreatic dysfunction and growth retardation, many phenotypic features often present at birth.

Phenotype and clinics

Intermittent neutropenia is the most common haematological finding (85-100%); in addition aplastic anemia (80%), increased hemoglobin F levels (80%), thrombocytopenia (25-85%) and impaired neutrophil chemotaxis, B- and T-cell defects can be found.

Fluctuating or persistent exocrine pancreatic dysfunction (with low serum amylase in 50-75%, low serum trypsinogen in 70-98% and abnormal pancreatic stimulation test in nearly 100%).

Growth retardation (shortness 60%, weight 50%, microcephalus <50%).

Other manifestations include delayed puberty, rib and thoracic bone abnormalities 30-50%, metaphyseal dysostosis 50-75%, dental dysplasia, hepatomegaly 10-60%, elevated liver transaminases 50-75%, Ichthyosis severe and recurrent viral, bacterial and fungal infections 50-75% and developmental delay.

Neoplastic risk

The risk for AML in SDS is estimated to be 15-25%. MDS has been found in small cohorts of SDS patients in 10-44%. The predilection to malignant myeloid transformation is higher in SDS patients with

evolving pancytopenia and can already occur during infancy.

Treatment

Pancreatic insufficiency can be treated with pancreatic enzyme replacement. Periodic monitoring for the occurrence of haematological manifestations and supportive care for pancytopenia are mandatory. GCSF is used for individuals with severe neutropenia and recurrent infections. Because of the possible underlying liver abnormalities androgen-therapy is not recommended. Bone marrow transplantation from a family- or alternative donor is the only curative option for severe bone marrow failure and is recommended in SDS patients with severe pancytopenia and evolving haematological malignancies.

Prognosis

Morbidity and mortality in infancy is related to infections, maldigestion and malabsorption and thoracic dystrophy. Pancreatic insufficiency that can be severe in infancy improves with increasing age in up to 50% of patients. In older children and adults, the main cause for morbidity and mortality are haematological. MDS and AML in patients with SDS has a poor prognosis, with a survival rate of < 20%.

Cytogenetics

Inborn conditions

Rare reports of increase in spontaneous chromosomal breakage.

Cancer cytogenetics

Clonal aberrations are common and frequently involve chromosome 7, typically in form of i(7)(q10).

Del(20q) represents the second most common

aberration, often occurring as secondary event to i(7)(q10).

Clonal aberrations need not indicate imminent transformation to MDS/AML and can be transient in nature.

Over 60% of transformed cases will have an abnormal clone that includes aberrations of either chromosome 7 and/or del(20q).

Other findings

Note

Additional reported findings.

Over-expression of p53 protein.

Abnormal telomeric shortening.

Increased apoptosis mediated through the Fas pathway.

Genes involved and proteins

SBDS

Location

7q11

DNA/RNA

Description: 5 exons spanning 7.9kb.

Protein

Description: Predicted protein is 28.8 kD.

Function: Member of highly conserved protein family of unknown function.

Mutations

Germinal: Various mutations have been described, including mutations resulting in stop codons and simple amino acid substitution.

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