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Cancer Prone Disease Section

Review

Down syndrome

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ABSTRACT

Review on Down syndrome, with data on clinics, susceptibility to neoplasms, and the genes involved

Keywords
Down syndrome, leukemia, myeloid proliferations, trisomy 21

Identity

Other names
Trisomy 21

Note

Etiology

Down syndrome (DS) has an incidence of approximately 1 in 700 live births, and is the most common aneuploidy of the autosomal chromosomes. Down syndrome is caused by an extra copy of chromosome 21. Most cases (95%) are the result of nondisjunction, leading to three free copies of the chromosome; this nondisjunction usually occurs in maternal meiosis I, though maternal meiosis II and paternal meiosis II errors also do occur. There is an increased risk of this nondisjunction with increased maternal age.

Another 4% of cases are the result of an extra copy of chromosome 21 transmitted by translocation with an acrocentric chromosome (usually chromosome 14 or 21). These translocations may be present in the parent who has a balanced translocation such as t(14;21) or t(21;21), and represent a genetic risk of inheritance. However, most of the translocations occur de novo.

The remaining cases are usually due to mosaicism for trisomy 21 with a normal karyotype. These patients tend to have less severe phenotypes

Clinics

Phenotype and clinics

Many organ system abnormalities are associated with Down syndrome (DS):

Craniofacial dysmorphism: Most children are brachycephalic with a relatively flat occiput. They may have microcephaly with upslanting palpebral fissures, small noses, flat nasal bridge, inner epicanthal folds, hypertelorism, and small ears.

Central nervous system: Intellectual disabilities are present in most patients. Alzheimer disease develops in more than half of DS patients by the age of 60 years.

Cardiovascular: Endocardial cushion defects lead to atrioventricular defects (most common), with less common ventricular septal defects, atrial septal defects, and tetralogy of Fallot.

Respiratory: Some respiratory disorders include upper respiratory tract anomalies, obstructive sleep apnea, recurrent aspiration, and recurrent respiratory tract infections.

Hematologic: Individuals with DS often have an immunodeficiency, leading to increased risk of infection. Newborns have an increased risk of transient abnormal myelopoiesis, and children and young adults especially those between 1 and 5 years

of age have a marked increased risk of leukemia (see below under Neoplastic Risk).

Gastrointestinal: Duodenal atresia/stenosis, Hirschsprung disease, esophageal atresia, pyloric stenosis, and imperforate anus are identified in some DS patients.

Endocrine: Hypothyroidism often occurs in neonates. In older patients, hyper- or hypo-thyroidism may be present with or without diabetes mellitus.

Musculoskeletal: Hypotonia is present in many. Ligament laxity, including occipitocervical instability and atlantoaxial instability are also common. Joints may be hyperflexible. Hands can be notable for short metacarpals and phalanges and/or a single palmar transverse (Simian) crease. Fifth finger hypoplasia may also be present. Feet may demonstrate a wide gap between the first and second toes. Talipes equinovarus may also occur.

Eye/vision: Severe refractive errors are present in approximately half of the patients.

Hearing: Conductive, mixed, or neurosensory hearing loss is common.

Oral: DS patients may have macroglossia, with microdontia

Neoplastic risk

Those with Down syndrome have a decreased risk of most solid tumors. Exceptions include testicular cancer, including germ cell tumors. The risk of extragonadal and ovarian germ cell tumors is also reportedly increased in DS (Nizetic and Groet, 2012; Englund et al., 2013).

Transient abnormal myelopoiesis (TAM) is thought to occur in up to 30% of neonates with Down syndrome. Symptomatic in up to 10%, this disorder is characterized by increased blasts (usually megakaryoblasts) which can lead to hepatomegaly, splenomegaly, and respiratory distress. In these patients, somatic GATA1 gene mutations are present in the clonal population. TAM presents within the first 7 days of life and usually spontaneous resolves within 2-3 months. Some infants who are symptomatic may require chemotherapy.

The risk of acute myeloid leukemia in children with DS is 150 times greater than in the general population; the incidence of acute megakaryoblastic leukemia is 500 times more likely in the DS population (Creutzig et al., 1996; Hasle et al., 2000). This myeloid leukemia of Down syndrome (ML-DS) occurs between 1 and 4 years of age, with 16-30% of children also having a history of clinical TAM. Somatic mutations in GATA1 are also identified in ML- DS.

The risk of acute lymphoblastic leukemia (ALL) in DS is also elevated, estimated at 40 times greater in children aged 1-5 years with DS compared to those without DS of the same age (Hasle et al., 2000). Unlike those without DS, ALL in DS usually does not have the classic favourable or unfavourable cytogenetic abnormalities. These ALL of DS cases do often have CRFL2 gene rearrangements either with P2RY8, also in the pseudoautosomal region of Xp22.33/Yp11 (del(X)(p22.33p22.33) or del(Y)(p11.32p11.32)), or with IGH (immunoglobulin heavy chain locus), on 14q32 (t(X;14)(p22;q32) or t(Y;14)(p11;q32)) (Mullighan et al., 2009; Hertzberg et al., 2010). JAK2 activating mutations are present in approximately 20% of ALL of DS cases, usually with mutations at R683 in the pseudokinase domain (Bercovich et al., 2008; Kearney et al., 2009; Gaikwad et al., 2009). IKZF1 deletions are also often identified in ALL of DS (Hertzberg et al., 2010; Buitenkamp et al., 2012).

Treatment

Most cases of TAM (66-84%) will spontaneously resolve without the need for interventions (Klusmann et al., 2008; Gamis et al., 2011). Cytarabine (cytosine arabinose) may be employed in infants with life-threatening symptoms (Massey et al., 2006)

ML-DS requires chemotherapy, though at a reduced intensity compared to those without Down syndrome.

Those with ALL of DS are treated similarly to those with ALL without DS. These patients have an increased susceptibility and toxicity to methotrexate.

Evolution

The majority of DS patients with TAM will have spontaneous resolution without treatment within 2-3 months; however, 16-30% of infants may go on to develop ML-DS (Klusmann et al., 2008).

For Down syndrome patients in general, Alzheimer's disease develops in more than half by 60 years of age.

Prognosis

The mortality rate for TAM is approximately 15-20%, though approximately half of these deaths are related to other congenital abnormalities of Down syndrome (Klusmann et al., 2008; Gamis et al., 2011).

ML-DS has a better prognosis than myeloid leukemia without Down syndrome. However, these individuals are still at a high risk for infection-related deaths. (Lange et al., 1998; Gamis et al., 2003; Rao et al., 2006)

Compared to those with ML-DS, ALL of DS has an equivalent to poorer prognosis compared to those with ALL without DS. Some studies have shown increased induction failures, higher relapse rates, and increased therapy-related mortality in those with ALL of DS.

For Down syndrome in general, the median age of mortality has increased throughout the years, most recently reported at almost 60 years (Englund et al., 2013). The most common causes of death are

infectious diseases (mostly pneumonia), congenital malformations (such as heart defects), circulatory disease, and dementia (Englund et al., 2013).

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