Prader Willi syndrome

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Identity

Note
The Prader Willi syndrome (PWS) is characterized by diminished fetal activity, dysmorphic facial features, small hands and feet, marked hypotonia, neonatal feeding problems, thick saliva, hyperphagia and weight gain between the ages of 1 and 6, poor linear growth, short stature, hypothalamic dysfunction (obesity, absence of satiety, hypogonadism with cryptorchidism, abnormal temperature control and GH deficiency), cognitive difficulties and characteristic behavioural traits.

Inheritance
It is sporadic and familial cases are rare. The incidence is 1:10.000-15.000 births.

Etiology
PWS is genetically heterogeneous. The absent expression of the paternal activity in the critical region on chromosome 15 has been found in patients with PWS. In 70-75% of patients there is a deletion of the paternal 15q11-q13 chromosome (del15) and in about 25% there is a maternal uniparental disomy 15 (UDP15), and a small percentage of patients may have an imprinting center mutation or translocations involving chromosome15. In the 15q11-q13 region a lot of candidate genes are present. The C/D box small nucleolar RNA (snRNA) gene cluster HBII-85, IPW, PAR1, MAGEL2 and SNRPN genes is not expressed in patients with PWS and may be involved in the phenotype.

Clinics

Phenotype and clinics

Abnormalities
Growth: Intrauterine growth retardation, short stature due to a growth hormone deficiency.

At 1-3 years hyperphagia appears with rapid weight gain and obesity. The leptine levels are normal and ghrelin levels are significantly elevated, 3-4 fold higher in children with PWS than in general population.

Craniofacial characteristics: High prominent forehead, narrow bifrontal diameter, telecanthus, downslated fissures, downturned corners of the mouth, micrognathia, dysplasic ears and diminished mimic activity due to muscular hypotonia (fig.1).

Dermatological anomalies: Hypopigmentation-fair skin and severe skin-picking.

Limbs and skeletal anomalies: Small hands and feet (acromicria), bracydactyly, clynodactyly of fifth finger, delayed bone age especially in the limbs, related to growth hormone function and diminished bone mineral density.

Hypothalamic dysfunction: Hypogonadotropic hypogonadism with cryptorchidism and micropenis, delayed or incomplete gonadal maturation with delayed pubertal findings, short stature secondary to growth hormone deficiency, hyperphagia with absence of satiety and obesity (fig.2), temperature instability, central adrenal insufficiency.

Performance and behavioural problems: Hypotonia, sleep disorders, obsessive compulsive behaviour, possessiveness, stubbornness and mild to moderate mental retardation.

Tumors: Myeloid leukaemia cases are 40 fold higher in PWS patients than in the general population. There have also been cases of lymphoblastic leukaemia, seminoma, adult ovarian teratoma, hepatic tumours, Hodgkin lymphoma and type 1 multiple endocrine neoplasia.

Occasional abnormalities

Skeletal findings: Scoliosis, kyphosis and hip dysplasia.

Central nervous system: Ventriculomegaly, decreased volume of the parietal-occipital lobe, sylvian fissure polymicrogyria and incomplete insular closure.
Congenital and acquired hypothyroidism.

Evolution
Multidisciplinary management (paediatrician, endocrinologist, orthopaedic specialist, dietologist, cardiologist, psychiatrist etc.) is necessary. Growth hormone treatment and strict diet control have been reported to significantly modify the life of children with PWS. Testosterone therapy has resulted in the enlargement of the micropenis to normal size for age and hormonal substitutive therapy with testosterone or estrogens allows a complete pubertal development.

Prognosis
The patients have an increased mortality of 3% across all age groups but, if strict weight control is achieved, survival is improved. Diabetes and its complications, cardiac failure and respiratory disorders (respiratory insufficiency or infections) are major causes of morbidity and mortality in PSW patients.

References


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