Patient

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Angelman's Syndrome

This is a rare genetic disorder first described in 1965 by Harry Angelman (1915-1996), an English physician. The behavioural features of Angelman's syndrome (AS) include a happy demeanour, easily provoked laughter, short attention span, hypermotoric behaviour, mouthing of objects, sleep disturbance and an affinity for water.

Genetics

- AS is caused by a lack of expression of the maternally inherited UBE3A gene in the brain.
- This can be due to: [1]
    - Deletion of the AS critical region on maternal chromosome 15q11-q13 (the most common type).
    - Paternal uniparental disomy (UPD) for chromosome 15.
    - An imprinting defect causing lack of expression of the maternal copy of UBE3A.
    - Mutations in the maternally inherited copy of UBE3A.

- UBE3A is one of a small subset of human genes that are imprinted. This means that it is expressed, depending on parent of origin, in a tissue-specific manner. [2]
- In the brain, the paternally derived UBE3A gene is silenced, and only the maternally inherited copy is active.
- However, there is a subgroup of patients with a clinical diagnosis of AS for whom no abnormality of UBE3A can be identified. [1]
- In most cases the recurrence is extremely rare - less than 1%.
- However, some deletions are familial and carry a 50% risk of recurrence.
- When the UBE3A mutations are inherited from the mother's paternally acquired allele then the recurrence risk is also 50%. [3]

Prevalence

- Its prevalence ranges from 1:10,000 to 1:40,000. [4]
- Diagnosis is commonly made at age 3-7 years, when the clinical features and behaviours become apparent.

Presentation

Symptoms

- The prenatal course and birth are normal.
- There is normal head circumference at birth and there are no major birth defects.
- Developmental delay is apparent by 6 months.
- There is forward progression with no loss of skills once acquired.

Consensus criteria for clinical features [5]

Consistent features

Motor signs

- Functionally severe developmental delay.
- Gross motor milestones are delayed:
    - Sitting occurs by 12 months; walking at 3-4 years.
    - 10% fail to walk.

- Legs are wide-spaced and feet are flat and turned out.
- There are disorders of movement and balance with ataxia, and tremulous movement of limbs.
- There is jitteriness from 6 months with irregular, coarse movements that prevent walking, feeding and reaching for objects.
- There may be toe-walking or a mild prancing gait.
- They tend to lean forward or lurch when they run.

Communication

- There is speech impairment with no or minimal use of words.
- Receptive and non-verbal communication skills are better.
- Even in the highest-functioning cases conversation does not develop.
- Cases caused by UPD are clinically less severe, with a vocabulary of up to 30 words reported.

Behaviour

- There are unique behaviours - a combination of laughter and smiling, an apparent happy demeanour and excitable personality.
- Laughter is an expressive motor event and most stimuli will produce it.
- Hand-flapping is common, as is hyper-motor behaviour and short attention span, impairing social interaction.
- There is a tendency to pinch, grab and bite in older children.

Frequent features

Growth

- Delayed disproportionate head circumference growth.
- Absolute or relative microcephaly by age 2 years; 34-88% have absolute as defined as within the lowest 2.5% centile.

Epilepsy

- Epilepsy occurs in around 90% of cases and may present with multiple seizure types, including non-convulsive status epilepticus. [6]
- Seizures are often intractable and typically require broad-spectrum antiepileptic medications.
- The electroencephalography (EEG) shows high amplitude, bilateral spike and wave activity, which is symmetrical, synchronous and monorhythmic, having a slow wave component at two cycles per second.

Sleep

- Sleep disorders are also common, often characterised by abnormal sleep-wake cycles. [6]
- The sleep disorders may be related to abnormal serum melatonin profiles. [7]
- Poor sleep does not significantly interfere with daytime alertness.
- Sleep problems commonly diminish by late childhood, with continuing improvement through adolescence and adulthood.

Associated features

Motor

- Strabismus is present in 30-60%.
- Increased tendon reflexes.
- Uplifted, flexed arms when walking.
- Tongue thrusting and swallowing problems (leading to feeding problems in infancy).
- Movement disorders are nearly universal in those with AS, most frequently presenting with ataxia and tremor. [6]

Phenotype

- Hypopigmentation of the eyes and skin, typically in deletion-caused cases - sun-sensitive.
- Prominent mandible with a wide mouth and wide-spaced teeth.
- Flat occiput.

Behaviour

- Frequent drooling.
- Excess chewing/mouthing.
- Increased sensitivity to heat, and fascination with water.

Differential diagnosis

- There are several characteristics shared with autism. Many are given a secondary diagnosis of autism. However, children with AS tend to be highly sociable in contrast to typical autistic peers.
- There is significant overlap with Rett's syndrome.
- Swallowing and feeding problems may lead cases to present with failure to thrive, lactose intolerance or gastro-oesophageal reflux.

Investigations

- The brain is structurally normal on CT or MRI scan. However, if there is any abnormality it is usually mild cortical atrophy and/or mildly decreased myelination.
- In the presence of normal chemical, haematological, metabolic tests and normal brain imaging, high-resolution chromosome analysis, including material from both parents, is undertaken.
- Fluorescence in situ hybridisation (FISH) is able to detect 80-85% of all deletions.
- DNA methylation testing increases pick-up rate.

Management

General

Suggested interventions include:

- Behaviour modification programmes
- Speech therapy
- Occupational therapy
- Physiotherapy
- Parental training

Behavioral treatment may be a reasonable way to address sleep problems in some children with AS. [8]

Parents of children with AS have an increased risk of high levels of stress and mental health problems. [9] These need to be addressed and managed appropriately.

Education

The most common preschool education programme used is 'Portage'. [10] This provides particular help with language, socialisation, self-help skills and cognitive and motor skills in a step-wise fashion at home.

A *statement of special educational need* will be required for specialist provision after 5 years.

Pharmacological

- It is common that a combination of treatment with anticonvulsants is needed to control seizures. [1]
- Sodium valproate and clonazepam are the most effective medications and carbamazepine is one of the least effective. [6]
- Sleep patterns may be helped by melatonin.

Prognosis

They have good general health and a normal lifespan.

- Clinical features alter with age:
    - As adults there is improvement in sleep patterns and hyperactivity.
    - Frequency of seizures also diminishes and may stop.
    - Females can tend to become obese.

- There is normal sexual development.

Further reading & references

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