

Rett syndrome

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Abstract

Rett syndrome in girls is characterized by a serious and global developmental disorder affecting the central nervous system. It has been recently established that Rett syndrome is associated with mutation in MeCP2, a gene encoding methyl-CpG-binding protein 2 and located on the long arm of chromosome X, in region Xq28. A deceleration of head growth is observed after the first year of life, and corresponds to an important cerebral atrophy that is diffuse and affects mainly gray matter. The evolution follows a characteristic pattern in typical forms. The main clinical manifestation consists of hand stereotypies. Rett syndrome exists in different parts of the world. Prevalence in Europe has been estimated to approximately 1:15,000. Mutations in the MeCP2 gene have been recently reported in males with severe encephalopathies. No etiologic treatment is available. Nonetheless, it is important to propose symptomatic treatment when necessary as well as adapted educational therapy.

Keywords

Rett syndrome, central nervous system developmental disorder, hand stereotypies, MeCP2

Definition

Rett syndrome is a serious and global developmental disorder affecting the central nervous system.

It has been recently established that Rett syndrome is associated with mutation in the MeCP2 gene, which encodes methyl-CpG-binding protein 2 and is located on the long arm of chromosome X, in region Xq28.

Etiology

Genetic data

Since its first description, Rett syndrome has been observed to occur exclusively in girls; besides, the disease homogeneity was also compatible with a genetic disorder. In a more

recent analysis of exceptional familial forms, region Xq28 was suspected to be specifically

involved. A search for candidate genes identified MeCP2, encoding a transcriptional repressor whose role in regulation is not well established. The loss of function of MECP2 protein might result into overexpression of genes that, in turn, may have deleterious effects on the central nervous central system development. Although many MeCP2 mutations have been reported, no phenotype-genotype correlations have been clearly established.

Neuropathologic and pathophysiologic data

A deceleration of head growth is observed after the first year of life, and corresponds to an important cerebral atrophy, which is diffuse and

affects mainly gray matter. Moreover, the abnormal reduction of dendritic trees in some cortical areas, and their absence of specification in other areas, suggest an arrest of the afferentation that are needed for the pursuit of an harmonious cerebral development.

These observations can be related to some aspects of functional imaging. The available data have been mainly obtained using the SPECT technique (single photon emission computed tomography). In "Rett girls" explored at the age of 2-3 years, the perfusion pattern is similar to that obtained in infants 2-3 months of age: hypoperfusion in the frontal lobes and cerebral trunk. A decrease of pigmentation in the substantia nigra, suggestive of anomalies in the dopaminergic pathway, and a reduced cell number in the cholinergic system have also been observed. However, different studies carried out on metabolites of neurotransmitters report contradictory results. Proton NMR (Nuclear Magnetic Resonance) spectroscopy shows a decrease in N-acetylaspartate (NAA). The loss of function of MECP2 protein might intervene at the level of neurotransmitters.

Frequency

Rett syndrome exists in different parts of the world. The prevalence in Europe is about 1:15.000.

Clinical description

Diagnosis is based on clinical signs. Some of them are considered as essentials.

Diagnosis criteria

essential criteria

The essential criteria are the followings:

- Apparently normal prenatal and perinatal period;
- Apparently normal psychomotor development until 6 months of age;
- Normal head circumference at birth;
- Deceleration of head growth (between 5 months and 4 years of age);
- Loss of acquired purposeful hand skills between 6 and 30 months of age, that is temporally associated with communication dysfunction and social withdrawal;
- Development of severely impaired language associated with a severe psychomotor retardation;
- Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and "washing"/rubbing;
- Appearance of gait apraxia and truncal apraxia/ataxia between 1 and 4 years of age;
- Diagnosis tentative until 2 to 5 years of age.

Supportive criteria

Supportive criteria include:

- Breathing dysfunction: periodic apnea during wakefulness, intermittent hyperventilation, breath-holding spells, and forced expulsion of air or saliva;
- EEG abnormalities;
- Epilepsy ;
- Spasticity, often associated with muscular atrophy and dystonia;
- Vasomotor disorders;
- Scoliosis;
- Growth retardation;
- Hypotrophic, small feet;
- Frequent shortening of the fourth metacarpal and/or metatarsal revealed by radiographs of the extremities;
- Bruxism;
- Impaired sleep pattern from early infancy.

Exclusion criteria

Exclusion criteria have been defined. They correspond to:

- Intrauterine growth retardation;
- Visceromegaly or signs of storage disease;
- Retinopathy or optic atrophy;
- Microcephaly at birth;
- Evidence of perinatally acquired brain damage;
- Existence of identifiable metabolic or other progressive neurologic disorder;

Acquired neurologic disorders resulting from severe infections or head trauma.

Evolution

The signs suggestive of the diagnosis are also associated with a particular pattern of evolution that is characteristic of the disease. Different progressive stages have been identified:

Early onset stagnation

This stage begins between 6 and 18 months of age and is characterized by:

- developmental stagnation;
- reduced interest in games;
- hypotonia;
- slowing of head growth.

This stage lasts for few months.

Rapid regression ("destruction")

The start occurs between 1 and 3 years of age. This stage is characterized by:

- rapid behavioral regression and deterioration;
- loss of purposeful hand skills;
- convulsive crises;
- hand stereotypies;
- autistic manifestations;

- loss of language skills;
- awkward movements;
- insomnia;
- behavior of self-mutilation

This stage lasts from a few weeks to a few months.

Relative stabilization

This stage starts between 2 and 10 years of age and is characterized by:

- severe mental retardation;
- regression of autistic traits;
- improvement in social interactions;
- convulsive crises;
- characteristic hand stereotypies;
- spasticity, ataxia, apraxia;
- breathing dysfunctions.

This stage lasts from a few months to a few years.

Late motor deterioration

This stage starts after 10 years of age and is characterized by:

- loss of motor functions (wheelchair);
- scoliosis, muscular atrophy, rigidity;
- marked pyramidal and extra-pyramidal symptoms;
- growth retardation;
- absence of language;
- improvement of eye contact;
- epilepsy less severe;
- trophic disorders.

This stage lasts for several years.

Atypical forms

The stages described above correspond to the most common clinical expression of this syndrome. Beside, other clinical manifestations can be found:

- more severe forms with congenital onset or with early-onset epilepsy;
- less severe forms;
- milder forms (forme fruste) with late regression, with preserved speech.

The diagnosis of these forms was previously made cautiously, but can now be confirmed by the identification of mutations in *MeCP2* gene.

Forms in males

The same genetic anomaly has been found in boys affected with encephalopathies of variable expression. The clinical picture, which is more severe and less homogeneous, is not comparable to that observed in females, and does not correspond to Rett syndrome.

Management including treatment

No etiologic treatment is available. Nonetheless, a symptomatic treatment must be proposed

when necessary (anti-epileptic drugs, specific monitoring for scoliosis, sufficient nutritional intakes, especially calcium intakes...). In addition, educational therapy must be adapted to each affected child. The French association for Rett syndrome provides precious help in this matter (<http://www.syndrome-de-rett.org/>).

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