X-LINKED INTELLECTUAL DISABILITY

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ABSTRACT

The intellectual disability is found in approximately 2–3% of the population in a mild-to-moderate form and 0.5–1% in a moderate-to-severe form. The mutations on the chromosome X are responsible for both syndromic and non-syndromic intellectual disability. In the syndromic forms behavioral disorders, autism and/or seizures are frequent.

***Key words**: intellectual disability X-linked, syndromic forms, dysmorphic features.*

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Introduction

The intellectual disability is found in approximately 2–3% of the population in a mild-to-moderate form and 0.5-1% a moderate-to-severe form[1].

The etiology can be different (unknown and environmental causes[2], chromosomal anomalies[3-6], genetic mutations[7], prenatally, perinatally, or postnatally causes etc.) and a careful anamnesis is necessary for a correct diagnosis.

When in a single family are more males with intellectual disability in pedigree of three generations, we suppose that it is caused by X-linked pathology, even if the clinical diagnosis of intellectual disability X-linked (XLID) is usually a diagnosis of exclusion of other causes of developmental delay in male.

Intellectual disability is more common in the male rather than in the female population, due to mutations on the X chromosome[8-10].

XLID is generally divided into syndromic forms, in which intellectual disability is only one of a large set of symptoms, and non-syndromic forms, in which intellectual disability is the only manifestation of the pathology[1].

The syndromic forms are prevalent, and about one half of XLID patients also manifest autism and/or seizures. To date, more than 150 XLID syndromes have been characterized and 102 XLID genes have been identified, accounting for 81 of these syndromes[8].

The XLID genes encode for proteins that are highly expressed in the brain, especially in the hippocampus, a region that plays a key role in learning and memory.

We report the data for three X-linked syndromes with intellectual disability.

Fragile X syndrome

Fragile X syndrome is a rare genetic disease associated with typical dysmorphism and mild to severe intellectual deficit that may be associated with behavioral disorders.

The clinical phenotype is variable. Prevalence is estimated at approximately 1/2,500 (prevalence of the full mutation allele) to 1/4,000 (prevalence of symptomatic cases)[11] for both genders.

The majority of males with Fragile X syndrome reveal significant intellectual disability (for-

merly referred to as "mental retardation"). Disabilities in Fragile X syndrome include a range from moderate learning disabilities to more severe intellectual ones. In males, the disease occurs during childhood with delayed developmental milestones (motor and/or language delay)[12,13]. In males and in 50% of females, intellectual disorders associated with behavioral problems and/or dysmorphic features appear. Behavioral characteristics can include attention deficit / hyperactivity disorder (ADD/ADHD), autism and autistic behaviors, social anxiety, hand-biting and/or flapping, poor eye contact, sensory disorders and increased risk for aggression[14-16]. Mood disorders, anxiety and aggressive behavior can be present[17]. In females, intellectual and behavioral disorders are mild (emotional and learning problems). Physical features may include large ears, long face, soft skin and large testicles (called "macroorchidism") in postpubertal males. Connective tissue problems may include ear infections[18], flat feet, high-arched palate, double-jointed fingers and hyper-flexible joints. Fragile X is caused by a "full" mutation in the fragile X mental retardation 1 (FMR1) gene, which creates a protein called "fragile X mental retardation protein" (FMRP). Nearly all cases of fragile X syndrome are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the FMR1 gene. Normally, this DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormally expanded CGG segment turns off (silences) the FMR1gene, which prevents the gene from producing FMRP. Loss or a shortage (deficiency) of this protein disrupts nervous system functions and leads to the signs and symptoms of fragile X syndrome[19]. Premutations are associated with phenotypes distinct from Fragile X syndrome including a risk of premature ovarian insufficiency in women, and the fragile X-associated tremor/ataxia syndrome. In some rare cases, Fragile X syndrome was shown to result from intragenic FMR1 point mutations rather than expansion of a CGG repeat. One function of the FMRP protein in the brain is to put the brakes on another protein in the brain, called "metabotropic glutamate receptor 5" (MGluR5). MGluR5 tells theneuronsto growdendrites, which are long, narrow parts that allow them to attach to other neurons. When the dendrites are the right size and shape, FMRP makes MGluR5 tell the neurons to stop. When FMRP is missing, the dendrites grow wild and uncontrolled. Fragile X syndrome is an X-linked dominant disorder with reduced penetrance in females. Genetic counseling should be offered to families of an affected individual in order to explain the mode of inheritance of the mutations (there is a 50% recurrence risk in premutated females). Prenatal diagnosis is possible on samples of chorionic villi or amniotic fluid. Most patients with fragile X syndrome generally have a normal life span.

New targeted treatments for Fragile X syndrome (mGluR5 antagonists, GABA A and B agonists, minocycline) are now being studied.

Alpha thalassemia - X-linked intellectual deficit syndrome

X-linked alpha thalassemia mental retardation (ATR-X) syndrome is a rare, inherited condition characterized by severe intellectual disability, characteristic facial features, genital abnormalities and alpha thalassemia[20-22].

Female carriers are usually physically and intellectually normal.

The phenotype is usually characterized by distinctive craniofacial features, genital anomalies, severe developmental delays, hypotonia, intellectual disability, and mild-to-moderate anemia secondary to alpha-thalassemia associated with spasticity or seizures, and growth retardation with midface hypoplasia and skeletal abnormalities and gastro-esophageal reflux that may cause death[23]. Craniofacial abnormalities include microcephaly, telecanthus or ocular hypertelorism, small nose, tented upper lip, and prominent or everted lower lip with coarsening of the facial features over time.

This syndrome is X-linked recessive and results from mutations in the ATRX gene, which encodes an ATP-dependent chromatin-remodeler. This disease results in severe disability and shortened lifespan. The best way to diagnose this condition is to identify a gene mutation in the affected individual through molecular genetic testing of the ATRX gene. Genetic counseling can be offered to families.

Rett syndrome

Rett syndrome is a genetic disorder that affects approximately 1 in 12,000 females (it is rarelyseen in males). Rett syndrome primarily affects females, making it one of the most common genetic causes

of severe intellectual disability in females.

It causes severe physical and mental disability that begins in early childhood.

The changes typically appear in the first 6-18 months of the infant's life. These include:

- a general slowness in development;
- floppiness;
- difficulty in feeding;
- abnormal hand movements (such as repeatedly making wringing, clapping or washing motions with the hands);
- less interest in social contact and eye contact;
- not very interested in toys;
- walking awkwardly and poor co-ordination of trunk and limbs.

The "rapid destructive stage", usually begins between the ages of one and four and may last for weeks or months.The children will gradually or suddenly start to develop severe problems with communication, language, learning, co-ordination and other brain functions[24-26].

Despite the identification of mutations in the X-linked gene methyl CpG-binding protein 2 (MECP2) in the majority of Rett syndrome patients, the etiology remains unclear. More recently mutations in two other genes, cyclin-dependent kinase like 5 (CDKL5) and Netrin G1, have been identified in patients with a clinical phenotype that strongly overlaps with Rett syndrome. Life expectancies are not well studied, although survival at least until the mid-20s is likely. The average life expectancy of a girl with Rett syndrome may be mid-40s. Death is often related to seizure, aspiration pneumonia and malnutrition[27,28].

Conclusion

Management of XLID is symptom-based and requires a multidisciplinary approach, which should be combined with speech therapy, sensory integration occupational therapy, individualized educational plans, and behavioral interventions. Genetic counseling and prenatal diagnosis can be offered to families.

diabetic patients independently of HT and heart failure. Prospective studies with a larger cohort are now needed to observe the effects of CT-1 treatment in a diabetic population.

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