Genetics of learning disability

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Abstract

A significant proportion of children with learning disability will have an underlying genetic cause. The genetic aetiology of learning disability is broad and includes chromosomal abnormalities, copy number variants, single gene, mitochondrial and imprinting disorders. New genetic technologies are increasing the likelihood that a diagnosis will be made in a child with a learning disability. This provides information on prognosis and complications, thereby facilitating optimal management for the child and genetic counselling for the family. Here we provide an overview of the genetics of learning disability and a clinical approach to investigating a child with a learning disability. The clinical features and management of a number of specific genetic conditions of particular relevance to paediatricians are described.

Keywords CGH microarray; fragile X; inborn errors of metabolism; intellectual disability; learning difficulties; learning disability

Introduction

Learning disability (LD) is a serious lifelong condition and a common reason for diagnostic assessment by paediatricians. There is an underlying genetic cause in a significant proportion of children with a LD. Recent developments in genomic technologies have increased the likelihood that a diagnosis will be reached in a child with a learning disability. Making a diagnosis is vital for understanding a child's condition and guiding optimal management for that child. It also enables accurate genetic information to be given to parents and other family members about the chance of recurrence and opens up the possibility of prenatal diagnosis (PND) and pre-implantation genetic diagnosis (PGD).

Definition

The terms LD, learning difficulties and intellectual disability are often used interchangeably, with LD being the preferred term in the Department of Health in the UK. 'Mental retardation' is a historical term that is now seldom used. The World Health Organization (WHO)'s Working Group on the Classification of Intellectual Disabilities for ICD-11 has proposed the use of the term intellectual developmental disorders, which recognises LD as both a health condition and a disability.

LD can be defined by IQ, indicated by a performance score more than 2.5 standard deviations below the mean on psychometric testing. An IQ between 50 and 70 is classified as mild LD (MLD) and less than 70 severe LD (SLD). However, the use of functional deficit as a measure of LD is in many ways more helpful. The ICD-11 Working Group has proposed that intellectual developmental disorders are defined as 'a group of developmental conditions characterized by significant impairment of cognitive functions, which are associated with limitations of learning, adaptive behaviour and skills.'

LD is distinct from global developmental delay (GDD). GDD is the term applied to children under the age of 5 years who have significant functional delay in two or more developmental domains (motor, speech and language, cognition, personal/social), whereas LD applies to individuals over 5 years of age. However many children with GDD will go on to have LD. LD can be divided into syndromic and non-syndromic forms. In syndromic intellectual disability, the disability is associated with a clear clinical phenotype which may include dysmorphic facial features or congenital anomalies. The term non-syndromic LD is used when the disability is the sole clinical feature. Behavioural problems such as autism and hyperactivity are frequently seen with LD, but are not a core component of LD and are considered associated features.

Epidemiology

LD represents a significant challenge to public health. The prevalence of LD in is estimated to be between 1% and 3% and is thought to be twice as common in low and middle income countries compared to high income countries. There is an excess of males, largely due to X-linked causes of LD, in both MLD and SLD.

SLD is estimated to have a prevalence of between 0.3% and 0.5% and occurs equally across social groups. Many of these individuals have associated health problems, a reduced life expectancy, and will require life-long care. MLD is more common and some individuals represent the lower end of the normal distribution of IQ. There is an inverse socioeconomic bias, with a higher prevalence of MLD in socially disadvantaged groups.

Pathology

Genetic factors have been estimated to be the main cause of LD in around 50% of all SLD and 15% of patients presenting with MLD. In most cases (70–80%) a cause for MLD cannot be identified. There are many environmental factors that can cause or contribute to LD, either antenatally, perinatally or postnatally. These include congenital infection (e.g. rubella, CMV, toxoplasma), teratogens (e.g. alcohol, sodium valproate), birth asphyxia, complications of prematurity and maternal phenylketonuria.

The genetic aetiology of LD is extremely broad. It includes chromosomal abnormalities (e.g. trisomy 21), copy number variants (CNVs) (e.g. 1p36 microdeletion), single gene disorders,

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which may be autosomal dominant, autosomal recessive, or X-linked, imprinting disorders and mitochondrial disorders. There are thousands of specific disorders in which LD is a feature and this list is continually expanding. As the number of novel genes increases, our understanding of the pathogenesis of LD has also improved. Many of these genes fall into distinct groups with roles in neurogenesis, neuronal migration, cellular signalling cascades, or regulation of transcription or translation. Metabolic causes of LD, thought to account for 1%–5% of individuals, are of particular importance as a number of these conditions are now treatable for example through dietary restrictions or enzyme replacement therapy.

Approach to the investigation of a child with LD

History

The history should include a three generation family tree with specific questions about parents' educational achievement, family history of LD, consanguinity, and previous pregnancy losses. The family history may reveal a vital clue, for example an X-linked pattern of inheritance. However the absence of a family history does not exclude a genetic cause. The details of the pregnancy and birth, including antenatal history of alcohol and prescription and recreational drugs, should be taken with a thorough but sensitive approach. Developmental milestones and educational history are of great importance. A history of regression should be specifically asked for and associated behaviours such as autism noted. A full medical history should be taken with particular attention to any neurological problems including seizures, growth, puberty, vision and hearing.

Examination

The height, weight and head circumference should be measured and plotted on a growth chart. Microcephaly, macrocephaly, short stature or overgrowth may indicate a syndromic diagnosis. A full examination should be performed, with particular attention to dysmorphic features, congenital abnormalities and neurological signs. The presence of hepatosplenomegaly suggests a metabolic storage disorder. Careful examination of the skin is indicated to look for signs of neurocutaneous disorders such as neurofibromatosis type 1 (NF1) or tuberous sclerosis (TS), or signs of chromosomal mosaicism. A clinical phenotype may change with age, so that early photographs may be helpful, as may be review at an older age, if no diagnosis is made initially.

Investigations (Summarised in Table 1)

Investigations should be guided by the history and examination findings. In the absence of a clinical suspicion of a particular disorder, CGH microarray should be performed. Testing for Fragile X syndrome (FRAX) should be performed in males or females with LD particularly if there is a family history suggestive of the diagnosis, or the patient has any physical or behavioural characteristics of FRAX. CGH microarray has taken the place of the karyotype as the first line chromosomal test (see Figure 1). This is an advance in technology that allows the detection of much smaller chromosomal imbalances (microdeletions and microdeletions) than was previously possible through microscopic karyotype analysis. Since the advent of this technology, many new intellectual disability syndromes have been described. The likelihood of detecting a pathogenic CNV is greater in patients with syndromic learning disabilities.

There are an increasing number of CNVs labelled as susceptibility loci for LD. Individuals carrying a susceptibility CNV have an increased chance of having a LD, however some will be asymptomatic. For example, 16p11.2 microduplications are associated with an increased susceptibility to LD and mental health problems, but many individuals with the microduplication do not have these difficulties. There are also many benign CNVs not known to cause disease seen in healthy individuals. Our knowledge of these CNVs is increasing, but it is not always possible to be sure if a CNV is pathogenic, a susceptibility locus or benign. Parental studies may be helpful in establishing the pathogenicity of a CNV and these issues should be discussed with parents when taking consent for testing.

If CGH microarray does not identify a diagnosis, the possibility of an inborn error of metabolism should be considered. Approximately two-thirds of treatable metabolic disorders can be identified by the screening tests listed in Table 2. Other investigations should be considered depending on the patient's presenting features. Boys with Duchenne muscular dystrophy may present with developmental delay, and a normal creatine kinase will exclude this diagnosis. Congenital hypothyroidism is screened for on the newborn blood spot and therefore only needs repeating if signs of hypothyroidism are present. MRI brain scans are not routinely recommended but may be helpful if macrocephaly, microcephaly, or neurological features are present. If there is a history or seizures or developmental regression, an EEG is indicated. There should be a low threshold for requesting review of the child's vision or hearing.

Referrals

Other investigations may be requested in conjunction with specialist services. If there is a clinical suspicion of a metabolic disorder, referral should be made to a metabolic specialist even if the screening investigations are normal. Developmental

Investigations for LD

First line investigations	Full blood count, urea and electrolytes, renal and liver function tests CGH microarray
Metabolic investigations	Bloods: ammonia, lactate, plasma amino acids, total homocysteine, acylcarnitine profile, copper and ceruloplasmin Urine: organic acids, purines and pyrimidines, creatine metabolites, oligosaccharides, glycosaminoglycans
Other investigations as indicated	Fragile X, CK, thyroid function tests, MRI brain, EEG, ophthalmology review, audiology assessment

Table 1