The estimated incidence of delayed psychomotor and mental retardation varies between 1% and 10%. There is no determined etiology of these disorders in 50% to 80% of all cases. Intellectual disability (ID) is a condition defined as a reduction of neurocognitive function (IQ below 70), and a significant reduction in the adaptability of social life, communication, work, rest, daily life, occurring throughout life, with the onset before the age of 18 years. For children under 5 years of use the term “global developmental delay” is adapted.. This delay refers to two or more domains of development (deficits in motor skills or so called small motor skills, speech / language, cognitive, social interaction / personal, dysfunction of everyday activities, benign dysmorphic disturbances, the abnormalities in neurological examination - hypotonia, spasticity, apraxia, microcephaly, macrocephaly). Intellectual disability affects between 1% to 3% of the population of children and adults worldwide. People with ID have a large number of co-morbidities, including neurological disorders, systemic problems, and behavioral disorders. Approximately 25-50% of cases is associated with genetic disorders. Diagnosis is putted usually before the age of 5 years old. More frequent affects boys and it may indicate a disorder linked to chromosome X [13].
The causes of intellectual disability are very heterogeneous and include environmental causes (eg, infection, exposure to teratogenic factors), genetic causes and multifactorial. In developed countries, more than 50% of the cases of intellectual disability genetic factor is considered as main cause due to chromosomal abnormalities or individual genes.

Currently cytogenetic studies play a major role in the evaluation of children with intellectual disability. These studies have a high diagnostic value. Availability and dissemination of this study encounter some limitations, technical and financial. This may lead to failures in the assessment of metabolism disturbances in newborns, identifiable genetic disease, for which curative treatment is available.

Learning disabilities are defined as a restrictions on intellectual (reasoning / solving / learning / problem) and adaptive behavior (conceptual / social / practical skills) and relate to children over the age of five and adults with onset before the age of eighteen years. The degree of disturbance and global learning difficulties can be divided into mild, moderate and severe. Diagnosis is to explain the etiology, to term prognosis, to discuss genetic mechanisms and the risk of intellectual disability, to evaluate treatment options and to avoid unnecessary diagnostic tests and provide support for the family.

In order to clarify these disorders, the algorithms of the study were elaborated. These include genetic testing, metabolic and radiological examinations in cases of disorder of unknown etiology.

The first step is to take the history and physical examination. A comprehensive medical history is to be extended to medical history spanning three generations. Gather family history of genetic disorders /intellectual disability, neurocognitive dysfunction, cerebral palsy, encephalopathy, hypotonia, seizure disorders, birth defects (such as heart defects, cleft palate), growth failure, other than a family inheritance dysmorphic features. The family history of recurrent miscarriages is also important [7, 14].

The age of the occurrence of developmental disorders, problems with learning, presence / absence of recourse to distinguish between congenital and acquired defects, a history of recurrent miscarriages, stillbirths, deaths are very important. Intellectual disability in boys, male relatives of mothers family with learning difficulties or developmental delay, can indicate a disorder associated with the X chromosome diseases. Phakomatosis such as neurofibromatosis type 1, tuberous sclerosis and Sturge-Weber syndrome, dysrafia core can often be associated with developmental disorders. Hepatosplenomegaly or cardiomyopathy can indicate inborn error of metabolism.

The development disturbances appear in mitochondrial cytopathies. Neurologic manifestation in infancy is associated with seizures (infantile spasms, myoclonic epilepsy), visual impairment, deafness, central dysphagia, apnoea and respiratory failure, diffuse muscular hypotonia, global developmental delay. In older children and young adults dystonia, cerebellar deficits, spastic diplegia, memory loss, cognitive deficits, progressive, hearing loss, dementia, autism, peripheral neuropathy, hypotonia and weakness, external ophtalmoplegia of all six muscle occur. Respirat-
ry insufficiency may result from myopathic involvement or from central respiratory failure or combination.

The second step is to study metabolic, genetic and neurological tests. The literature review conducted in 2012, identified 81 treatable inborn errors of metabolism that cause intellectual disability. Fifty-two factors (65%) are detectable by biochemical blood and urine tests, and the rest of the metabolic disturbances were establish by clinical symptoms and appropriate genetic tests, biochemical tests. Early diagnosis of a treatable form of intellectual disability is necessary, because the diet, vitamin supplementations, inhibitors, stem cell transplantation, gene therapy and other methods of treatment may prevent permanent damage to the brain and optimize the developmental effects.

Next steps in the diagnosis of a child with unexplained cause of intellectual disability requires consideration of current diagnostic guidelines, which recommend testing, such as testing eyesight and hearing, microarray chromosomes test and in some cases, the test for fragile X and neuroimaging.

Borderline Intellectual Functioning: Consensus and good practise guidelines (process proposed by the CONFIL 2007 consensus group to detect and diagnose Bordeline Intellectual Functioning –BIF):

1. Clinical history – aspect of development, examination and clinical observation, biomedical investigation.
2. Establishing IQ – verbal and/or manipulative tests
3. Cognitive assessment – Language, attention, memory, visual-spatial function, behavioural and emotional aspects
4. Bordeline intellectual functioning BIF?
5. Specific developmental disorders
6. Generalised neurodevelopmental disorders
7. Comorbidity: disorders of behaviour, anxiety, depression, psychosis

Definition of BIF by the CONFIL 2007:
- BIF is not a syndrom, nor a disorder, nor a disease. It is a heterogenous grouping of specific neurodevelopmental syndromes, disorders or disease and possibly of extreme variations of normality.
- BIF can be defined as a “health meta-condition that requires specific public attention”.
- The cognitive deficits that undrie overall IQ assessment are heterogeneous, so cognitive assessment of the individuals with BIF should not to be limited to IQ measurement.
- Not all the individuals with an IQ between 71 and 85 have limitations in activity and restrictions in participation. Consequently, a specific assessment of capacities and functioning is needed to make a diagnosis of BIF.
The diagnosis of a treatable form of intellectual disability is especially important for pediatricians, whose first objective is to provide early and effective treatment. Interdisciplinary collaboration in the field of metabolic diseases, genetics, pediatrics, neurology, psychiatry enable faster diagnosis.

Indications for study of intellectual disability: dysmorphism, congenital defects, unexplained seizures, psychomotor retardation or regression of development, hypotonia, abnormal growth, autism spectrum disorders (ASD). Autism is a heterogeneous group of neurodevelopmental disorders with onset in early childhood, characterized by different levels of functioning. The main areas of disorders are social relations, stereotypical behavior and interests. Many studies have shown abnormalities in the brain neurotransmission in people with autism. There is a possibility of coexistence of other disorders: mental retardation, epilepsy, attention deficit hyperkinetic disorder, sleep disturbances, anxiety. Epilepsy is a common co-morbidity of autism. These disorders lead to dysfunction of the anatomical structures of the brain that are responsible for stimulating specific cognitive functions. There is a need of the complex multidisciplinary care.

All patients should be considered the primary screening, eye and hearing test, test for intoxication with lead, consult a genetic.


For children aged over 2 to 3 years with isolated global delay development /intellectual disability, with or without ASD, in the absence of progress in developmental disorders, it is recommended basic blood tests (including the muscle enzymes boys to identify cases of Duchenne muscular dystrophy), homocysteine test, thyroid hormones. In children aged 2 to 3 years with expect progression comprehensive neurometabolic study are indicated.

Genetic studies, including high-resolution karyotype and the fragile-X should be performed in every case of a global developmental delay or intellectual disability.

Intellectual disability (ID) is characterized by genetic diversity. Several hundred genes are associated with monogenic form of ID and that complicates molecular diagnostics.

If convulsions or hypotonia are present metabolic consultation is recommended. Metabolic testings to perform:
- plasma amino acids
- urinary organic acids
- acyl plasma
- glycosaminoglycans
- carnitine profile
- oligosaccharides
- purine
- pyrimidine
- metabolites GAA / creatinine
- aCGH test if ID or dysmorphism are present
The global developmental delay and intellectual disability - diagnostic difficulties

Imaging CT / MRI with / without spectroscopy – must be consider if focal neurological symptoms, microcephaly, convulsions, hypotonia, or macrocephaly are present. Differential diagnosis: environmental factors (severe prematurity, malnutrition, prenatal exposure, eg, ethanol, antiepileptics, lead poisoning, meningitis, neglect / abuse, metabolic disorders, hearing or vision problems, thyroid disease.

Radiologic testings to perform:
MRI brain is recommended when the GDD / LD are one of the following:
- severe / profound learning difficulties or
- with early onset seizures or
- moderate or severe motor delay or
- spasticity, ataxia and movement disorders or
- features asymmetrical motor or
- abnormal head size.

Compared to computed tomography (CT), MRI is more sensitive in the detection of specific disorders of the brain. CT contributes to the etiological diagnosis of GDD of about 30% of cases and may have advantages compared to MRI in certain circumstances, such as congenital infections [14].

Algorithm of Developmental Delay (DD) or Intellectual Disability (ID) Testing (by ARUP Laboratories) [1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 15]:
1. Risk factors:
   - Family history of genetic disorders / ID
   - Neurocognitive dysfunction
   - Cerebral palsy and static encephalopathy
   - Hypotonia
   - seizure disorder
   - Birth defects (eg, cardiac defect, cleft palate, club feet)
   - Growth abnormalities
   - Nonfamilial dysmorphic features
   - Family history of recurrent miscarriages

2. Evaluation for DD / ID, identify family history of risk factors:
   - Sufficient minor or major dysmorphic (atypical) features
     - if yes, refer for genetics consultation
     - if no, estimate of presence of microcephaly, macrocephaly, focal findings on neurologic exam, cerebral palsy, hypotonia, seizures, autism / ASD:
       - if yes, order MRI / CT, then may want to consider cytogenetic and / or molecular testing based on clinical presentation and genetics consultation
       - if no, may want to consider cytogenetic and / or molecular testing based on clinical presentation and genetics consultation
   - Episodic deterioration
     - Metabolic testing, refer for metabolic consul
   - Family history of metabolic disorder
- if yes, metabolic testing refer for metabolic consul
- IF male with neurocognitive dysfunction order Fragile X (FMR1) With a Reflex Methylation Analysis. Note: test more likely to be positive in the following cases:
  - Physical features characteristic of Fragile X
  - Family history supportive of X-linked ID
  - Maternal family history of premature ovarian failure, ataxia and / or tumor

3. Negative metabolic testing and family history of metabolic disorder:
- Cytogenomic SNP Microarray or Cytogenomic SNP Microarray Buccal Swab - first line testing for most developmental delay syndromes or
- Cytogenomic SNP Microarray with Five-Cell Chromosome Study, Peripheral Blood - useful if chromosome and array tests would otherwise have been ordered concurrently

Other available testing:
- X Chromosome Ultra-High Density Microarray (Consider this test if FMR1 testing is negative)
- Chromosome Analysis, Peripheral Blood
- Chromosome FISH Metaphase Fragile X (FMR1) With Reflex is Methylation Analysis
- Rett Syndrome (MECP2) Sequencing and Deletion / Duplication
- Rett Syndrome (MECP2) Full Gene Sequencing
- Rett Syndrome (MECP2) Deletion and Duplication
- Angelman Syndrome and Prader-Willi Syndrome by Methylation-Sensitive PCR
- Angelman Syndrome (UBE3A) Sequencing
- Angelman Syndrome and Prader-Willi Syndrome by Methylation-Sensitive PCR Fetal
- CDKL5 -Related Disorders (CDKL5) Sequencing and Deletion / Duplication
- CDKL5 -Related Disorders (CDKL5) Sequencing
- CDKL5 -Related Disorders (CDKL5) Deletion / Duplication
- PTEN -Related Disorders (PTEN) Sequencing and Deletion / Duplication
- X-Linked Intellectual Disability Panel, Sequencing, 76 Genes

1. Genetic consultation and treat symptomatically
   The etiology of symptomatic or unexplained global developmental disorders and learning disabilities remains a challenge for pediatricians and physicians adults. The precise diagnosis on the basis of the specific etiology may have implications for the treatment, prognosis. Many cases of global developmental delay and learning difficulties can be attributed to genetic disorders (25-50%) and metabolic disorders (1-5%).

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Metabolic disorders may result in developmental problems and it is important to quickly identify those that are susceptible to treatment. Neuroimaging study can identify the specific cause of the disorders associated with the process of learning disability in a few cases in the absence of abnormalities such as head size, epilepsy and disorders of motor. However, the efficiency of these tests is low. Therefore, genetic, metabolic and radiological examinations have become routine in the diagnosis of developmental disorders and intellectual.

The diseases with associated global developmental delay and intellectual disability:

- Prenatal encephalopathies of disruptive origin
- Congenital infections
- Teratogen – related encephalopathies
- Genetic encephalopathies
- Down syndrome
- Fragile-X syndrome
- Subtelomeric deletions
- Patau syndrome
- Chromosomal defects diagnosed by CGH array
- Tuberous sclerosis
- Congenital myotonic dystrophy
- Rett syndrome
- Dravet spectrum disorder
- Prader-Willi syndrome
- Angelman syndrome
- Neurofibromatosis type 1
- Inborn errors of metabolism
- Mitochondrial disease
- Lysosomal disease
- Perinatal and postnatal encephalopathies
- Brain tumor

**SUMMARY**

If any of these are present, they should be included detailed clinical accompany the application for metabolic studies:

1. Global development delay / Learning disability (public domain and degree of delay)
2. family history of metabolic disease
3. relationship
4. belonging to an ethnic group
5. dysmorphic features
6. hypoglycemia (glucose state requirements)
7. seizures
8. microcephaly / macrocephaly
9. hypotonia
10. hepatomegaly
11. eye Disorders
12. the hearing disorders
13. vomiting
14. sepsis
15. mechanical ventilation
16. intravenous (IV) fluids such as glucose
17. medications (IV / oral) such as dopamine antiepileptics
18. failure to develop (as if in feed containing medium-chain triglycerides (MCT), oil, or carnitine)
19. the sampling time from the last meal
20. lethargy
21. metabolic acidosis
22. raised plasma lactate
23. raised plasma ammonia
24. raised CPK levels

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ABSTRACT

Developmental disorders are a group of chronic diseases, which can be attributed to physical or mental disability. Global developmental delay and intellectual disability are the most common reasons for consultation in pediatric neurology. The reasons for these disorders may be different, genetic or metabolic. Diagnosis is easy when they are associated with cerebral palsy, epilepsy, blindness, profound hearing loss. It is more difficult in the case of coexistence of autism spectrum disorders. Genetic studies provide assistance in cases of disorders of unknown etiology.

STRESZCZENIE

Zaburzenia rozwojowe to grupa przewlekłych chorób, którym można przypisać upośledzenie fizyczne lub psychiczne. Globalne opóźnienie rozwoju i niepełnosprawność intelektualna są to najczęstsze powody konsultacji w neurologii dziecięcej. Przyczyny tych zaburzeń mogą być różne, m. in. genetyczne, metaboliczne. Postawienie rozpoznania jest łatwe gdy są związane z porażeniem mózgowym,
padaczką, ślepotą, głębokim niedosłuchem. Trudniejsze w przypadku współistnienia zaburzeń ze spektrum autyzmu. Badania genetyczne służą pomocą w przypadkach zaburzeń o niewyjaśnionej etiologii.

Artykuł zawiera 20857 znaków ze spacjami