KEYPOINTS IN INVESTIGATING THE CHILD WITH GLOBAL DEVELOPMENTAL DELAY AND INTELLECTUAL DISABILITY

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ABSTRACT

Objective. This paper highlights the main lines of etiological investigation of global developmental delay (GDD), mental retardation (MR) or intellectual disability (ID) and their specific order. GDD and MR/ID are chronic entities with onset during the developmental period, affecting personal, social, academic, occupational functions. Elucidating the etiology is important for establishing the management, for assessing the outcome, the recurrence risk, potential opportunities for prevention and for decreasing the psycho-emotional impact on families.
Material and method. Relevant literature was reviewed, currently being published recommendations for the diagnostic approach of children with GDD/MR, starting with a thorough history, a thorough clinical examination, then formulating a suspected etiology and including genetic, metabolic, neuroimaging testing.
Results and conclusions. Advances in genetics have changed the approach of children with unexplained GDD, increasing the rate of pathogenic chromosomal abnormalities identification. Comparative genomic hybridization is recommended as first-line investigation, with karyotyping as complementary. Sequencing allows the study of many genes involved in GDD and genetic consultation prioritizes the investigations. The identification of the etiologic diagnosis offers the possibility of establishing anticipatory, individualized management plans, in order to limit the complications and associated comorbidities, thereby improving the quality of life.

Keywords: developmental delay, mental retardation, cytogenetic, metabolic

INTRODUCTION

The child with intellectual disability requires permanent support from family, clinicians and educational personnel in order to attain developmental milestones corresponding to their age. The optimal approach of these children begins with establishing a correct etiologic diagnosis, thus enabling an individualized treatment plan, an anticipative tracking of possible complications and prognosis assessment that will facilitate family access to support groups, research studies and appropriate educational systems. This allows assessing the recurrence risk and even prenatal diagnosis in some cases. Most importantly, it helps parents to regain a sense of control and thus psycho-emotional balance, predictability over their family life, reducing their anxiety (1).

Global developmental delay (GDD) and mental retardation (intellectual disability, ID) represent an important part of developmental disabilities, chronic entities that start early during child development, typically before school age and are characterized by dysfunction of personal, self service, social, academic or occupational abilities (2).

Global development delay (GDD) is a significant delay (*significant* referring to lower than two or more than two standard deviations below the ref-

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erence norms for age) in at least two of the following domains of development: gross/fine motor, speech/language, cognition, social/personal behavior and activities of daily living (3). The term is used for children younger than 5 years, when clinical severity can not be assessed adequately, child development being a dynamic process, some mild forms of GDD recovering afterwards. For children over 5 years the term intellectual disability (ID) (4,5) is used and the application of intelligence tests is possible with results below 2 standard deviations for age, defined as an intelligence quotient (IQ) below 70 (2).

GDD prevalence is estimated to 1-3% in children under 5 years of age (4,6) correlating with the ID reported at about the same value 2%. (7)

ETIOLOGY

Various studies have attempted defining the etiology of GDD, covering a wide spectrum of acquired or genetic disorders, but remaining unknown up to a significant percentage – 20-62% (8). In an attempt to classify the main causes of GDD, these were described as: prenatal intrinsic (genetic/metabolic disorders, malformations of the central nervous system) and extrinsic (toxins/teratogenic agents, infections), perinatal causes (asphyxia, prematurity, neonatal complications) and postnatal (postnatal infections, toxic and psychosocial causes) (9).

Etiologic diagnosis has as its starting point a thorough history, a meticulous clinical neurological and dysmorphological examination and an analysis of behavioral phenotypes based on which clinical investigations will be carefuly scheduled. One third of the etiological diagnosis are obtained just after history and clinical examinations (10).

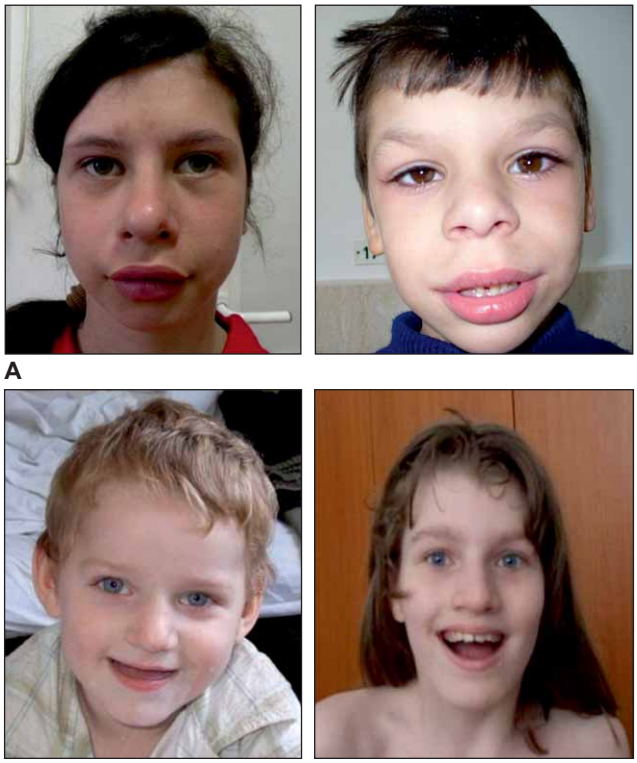
HISTORY AND CLINICAL EXAMINATION

Family history reagarding cognitive deficits, psychiatric disorders, malformations, epilepsy (11) occupies an important place in the diagnostic algorithm of a child with GDD. A family tree that includes at least 3 generations, allows the identification of other affected members with intellectual disabilities and reveals the mode of transmission – X-linked in cases where there are multiple males with mental retardation on the maternal side and autosomal recessive particularly in cases of consanguinity. Parents' age can raise the suspicion of chromosomal abnormalities (advanced age of the mother). Data on possible miscarriages must be obtained (possibly caused by unbalanced translocations or chromosome rearrangements), also about newborn deaths and cases of sudden death, and in case of multiple affected children of the same family the suspicion of toxic etiology will be investigated (maternal consumption of alcohol, exposure to teratogenic or toxic agents in the environment, such as lead) or metabolic (phenylketonuria, mitochondrial or peroxisome disease etc.) (11).

Personal history will contain information on birth (possible complications, birth weight, Apgar scores, postnatal adaptation), followed by evaluation of the moment and pattern of acquired milestones (head control, sitting position, walking independently, object-tracking, prehension, language, etc). It will be insisted on and noted the age at which the developmental delay was noticed, possible evidence of decline, the child's social insertion, aspects of behavior, including feeding and sleep patterns should be evaluated and also associated pathologies (eg epilepsy).

Clinical examination, essential in the elaborating of the investigations for children with GDD/ID must be carefully planned, with an emphasis on growth parameters – head circumference, height, weight, and cutaneous stigmata that might suggest a neurocutaneous disorder (*café au lait spots* – in neurofibromatosis, achromic spots – in tuberous sclerosis) and possible dysmorphic traits – constitutional particularities, the degree of similarity with family, associated congenital anomalies. Development in the field of dysmorphology improved describing phenotypes, bringing consistency and precision in communicating with those involved in genetic research, increasing the recognition rate with a decrease in diagnostic time, especially for the main microdeletion syndromes (del) – cri-du-chat (del chromosome 5), Williams syndrome (del chromosome 7), Angelman and Prader-Willi syndromes (del on chromosome 15), etc., cases in which the diagnosis suspicion points toward the specific testing. ID associated with these disorders is considered syndromic, unlike those of unknown etiology, withouth associated abnormalities or dysmorphism, which are considered non-syndromic.

Clinical evaluation will note any associated organomegaly (storage disease) or systemic disease (cardiomyopathy, liver disease, etc.) and will be completed by the neurological examination in order to reveal neurological signs and sensory impairment (visual disturbances, hypoacusis, deafness).



A

B

FIGURE 1. *Intellectual Disability/Syndromic Mental Retardation – From the cases of Pediatric Neurology Department of „Alexandru Obregia" Psychiatric Hospital, Bucharest.* ***A. Williams Syndrome*** *– classic phenotype: full cheeks, periorbital edema, wide mouth, protruding lower lip, small chin;* ***B. Angelman Syndrome*** *– classic phenotype: blonde hair, blue, deeply set eyes, mediofacial hypoplasia, wide mouth, often smiling.*

INVESTIGATIONS

1. Genetic Testing

Cytogenetics – classical and molecular techniques

In the context of technological development and advances in the field of genetics, the classical cytogenetic methods, **karyotyping** techniques, remain limited indications in GDD, although their importance can not be denied, with an average frequency of reported chromosomal abnormalities of 10% (12). High resolution karyotyping with G banding, which was the first line of investigation in GDD up to 2010, particularly if associated with facial dysmorphism and multiple congenital anomalies, has since lost diagnostic value and is currently indicated for patients with clinically identifiable chromosomal syndromes (Down, Turner, Edwards, etc.), with family history of chromosomal rearrangements, in case of infertility or multiple miscarriages. (13)

If a microdeletion/microduplication syndrome is suspected, **FISH** (fluorescent in situ hybridization), a technique of molecular cytogenetics, can be used as an initial test to confirm the diagnosis, this detecting, by binding to specific chromosomal regions, mainly deletions on chromosome telomeres, the second cause of GDD/ID after Down syndrome (14).

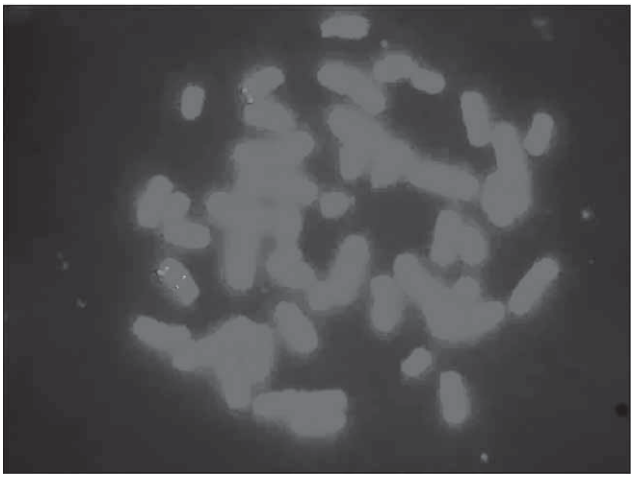
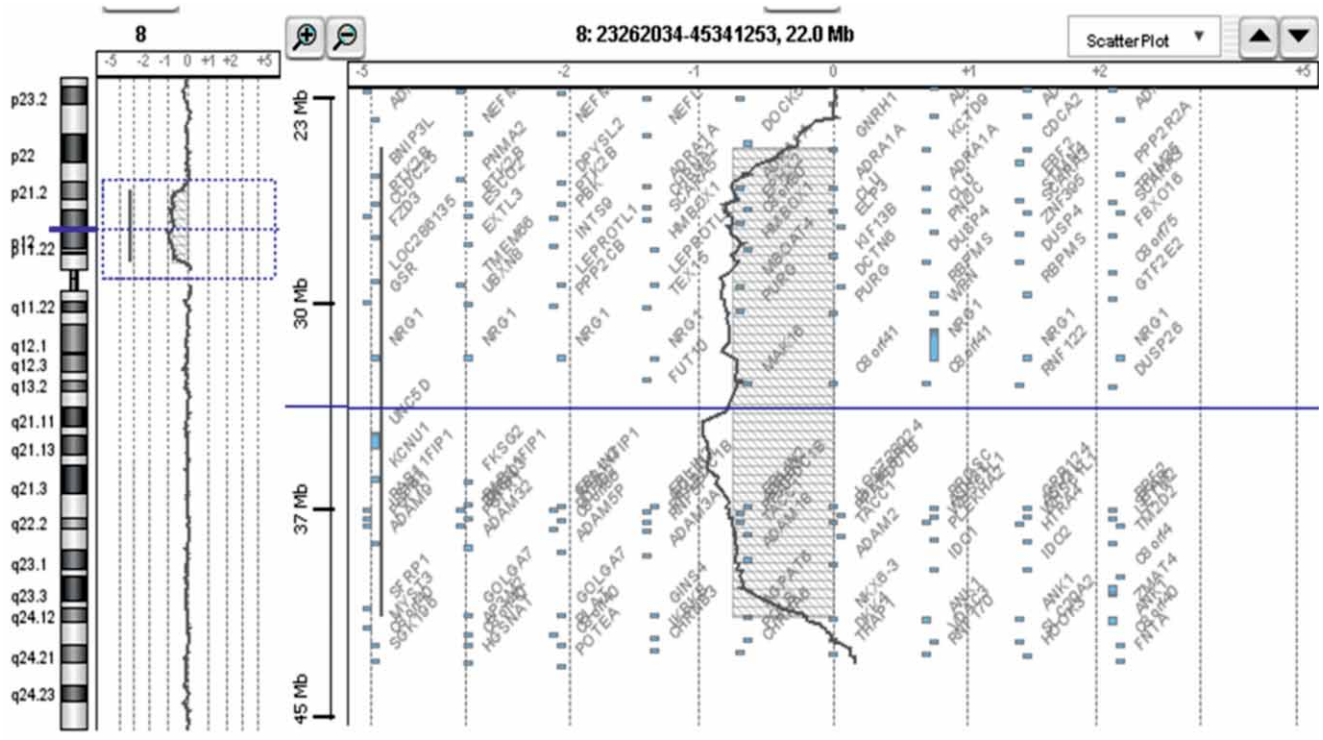


FIGURE 2. FISH *with a probe specific for Angelman Syndrome confirmed the deletion in region 15q11-13.*

The development of microarray technology is a huge step in the diagnosis of patients with ID/GDD, the most widely used technique being **array comparative genomic hybridization** (aCGH) technique. This is based on competitive hybridization of a mixture of fluorescently labeled nucleic acids (sample + reference), by computer processing being generated a profile of the sample, with loss or gain of genetic material called DNA copy number variation (CNV). Its significance may be pathogenic, benign or of uncertain significance. The Practice Guidelines of the American College of Medical Genetics recommended chromosomal microarray techniques as first-line investigation for patients presenting nonsyndromic ID/GDD nonsyndromic (13) (Fig. 3). Genetic anomaly detection rate is almost double than that of karyotyping (15), with an average rate of 12% (13).

Sequencing Techniques

Technological advances in genetic diagnosis bring to the forefront sequencing techniques as a method of detecting genetic abnormalities for many rare diseases. *Next-generation sequencing* (**NGS**) is thus available, which allows the simultaneous analysis of several genes associated with specific phenotypes/pathologies – epilepsy, mitochondrial disorders, X-linked ID or associated with distinct characteristics (micro-/macrocephaly, autism, seizures). Recently, whole exome sequencing (**WES**) and whole genome sequencing (**WGS**) developed,



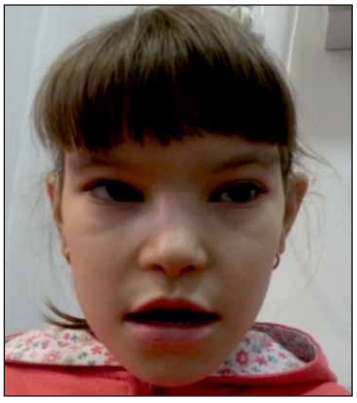


FIGURE 3. aCGH-46, XX, del (8) (p11.21p21.2) *– deletion in the short arm of chromosome 8 p, a girl with GDD and dysmorphism in a region which represents ~ 140 genes involved in neuropsychiatric disorders – autism, schizophrenia and neurodegenerative diseases, explaining the severe phenotype of the child (autism, retardation mental severely stressed dysmorphism): ADRA1A, CHRNA2, CHRNA6, DPYSL2, FGFR1, FZD3, etc.*

thus passing from their use in research to implementation in daily practice (16). It examines the „trios" – child with GDD and unaffected parents in order to identify de novo mutations in candidate genes for GDD/ID, demonstrating the essential role of these methods in elucidating genetic diagnosis in mental retardation.

2. Metabolic Testing

Typically, the metabolic disorders present, in addition to global developmental delay, also neurological (hypotonia, epilepsy, acute/recurrent encephalopathy, etc.) and systemic signs (coarse facial features, organomegaly, multiple organ dysfunction, failure to thrive), along with a progressive clinical picture, with regression pattern or episodic decompensation. The evidence available so far do not support routinely indication of metabolic testing, the incidence of these disorders in patients with TGD/DI ranging from 1-5% (12,17). Although there are no standard recommendations, there are checklists available in literature, containing „warning signs" (Table 1) and biological abnormalities that require analysis in this direction, as metabolic/respiratory acidosis, hyperammonemia, hyperuricemia, low levels of cholesterol (18).

Of particular importance is the identification of treatable metabolic diseases, with improved prognosis with treatment, currently 81 such disordres being identified (50 by „routine" laboratory testing) (19). Metabolic tests should be performed selectively, targeted, including, depending on availability, accessibility and degree of invasiveness: first line investigations which sholud be performed in every patient with ID, including biochemical tests, as ammonia, lactate, plasma amino acids, homocysteine level, total acylcarnitine, copper and ceruloplasmin (serum) and organic acids, purines and

TABLE 1. *Clinical abnormalities that may indicate the need for metabolic investigation*

Failure to appropriate growth
Psychomotor regres
Recurrent episodes of unknown origin
Coma/recurrent episodes of somnolence
Epileptic seizures
Ataxia
Hypotonia
Coarse facial features
Eye abnormalities (cataract, abnormal retina, ophtalmoplegia, etc.)
Unexplained deafness
Hepatosplenomegaly
Abnormal sexual differentiation
Arachnodactyly
Structural hair abnormalities
Bone abnormalities (dysostosis, punctate calcifications, occipital horns etc.)
Skin abnormalities (angiokeratoma, icthyosis, etc.)

pyrimidine, creatine metabolites, oligosaccharides and glycosaminoglycans (urine) and also second line tests (biochemical and molecular) (19) (Table 2).

TABLE 2. *Second line metabolic investigations – adapted from Van Karnebeek et al. (19) with permission*

Specific second line metabolic investigations – identifying up to 40% of treatable metabolic disorders
Biochemical/molecular investigations
Whole blood manganese Plasma Cholestanol Plasma 7-dehydroxy-cholesterol: cholesterol ratio Plasma pipecolic acid ann urine AASA Plasma Very Long Chain Fatty Acids Plasma B12 Vitamine & folate Serum and CSF lactate: piruvate ratio Enzyme activities (leucocytes): arylsulphatase A, biotinidase, glucocerebrosidase, fatty aldehyde dehydrogenase etc. CSF Aminoacids CSF Neurotransmitters CSF: plasma: glucose ratio Urine Deoxypyridonoline CoenzimeQ (fibroblasts measurements)
Molecular Tests: CA5A, NPC1, SC4MOL, SLC18A2, SLC19A3, PDHA1, PDHX, DLAT, SPR, TH*

*CA5A = carbonic anhydrase 5A; NPC1 = Niemann-Pick disease type C1; SC4MOL = sterol-C4-methyl oxidase–like gene; SLC18A2 = solute carrier family 18 (vesicular monoamine) member 2; SLC19A3 = solute carrier family 19 (thiamine transporter) member 3; PDHA1 = pyruvate dehydrogenase (lipoamide) alpha 1; PDHX = pyruvate dehydrogenase complex, component X; DLAT = dihydrolipoamide S-acetyltransferase; SPR = sepiapterin reductase; TH = tyrosine hydroxylase

3. Imaging

There is no current consensus as to the role of cerebral imaging for children with GDD, recommendations ranging from performing this investigation in all cases of GDD/DI to performing it only based on a rigorous clinical examination (20) as a second line investigation. Brain abnormalities can lead to the recognition of a specific cause for the GDD, but in many cases they are not sufficient by themselves to achieve this. As a technique, the magnetic resonance imaging (MRI) is preferred to the computed tomography (CT), as it is more sensitive and yields a higher rate of anomalies detection, with diagnostic implications (3). The rate of abnormal results vary greatly depending on the selection criteria of studied groups, the figures varying between selected groups of children with an abnormal head circumference (microcephaly, macrocephaly) or abnormal neurological signs and groups in which the imaging was performed as screening in children with GDD/DI.

4. Ancillary investigations

In addition to the investigations listed above, depending on the clinical picture, it might be useful to obtain muscle enzymes level (primary muscle disease can present at an early age as GDD), to explore thyroid function, as thyroid dysfunction is found in many genetic disorders (i.e. Down syndrome, DiGeorge syndrome), to explore the phosphocalcic metabolism (i.e. DiGeorge syndrome, impaired parathyroid hormone) and TORCH testing required for any newborn with neurologic abnormalities, microcephaly, vision and/ or hearing impairment (21). EEG is indicated for cases associated with seizures.

Current recommendations for the evaluation of children with GDD or ID are those of the Genetics Committee of the American Academy of Pediatrics (22), referring mainly to genetic evaluation and establishing the diagnostic steps and the roles and responsibilities for each family member and the medical community:

- To be performed first: complete medical history, the personal and family history on at least 3 generations and a clinical examination, assessment of dysmorphological abnormalities and neurological examination.
- If a diagnosis is certain, the family and medical home will be provided informations on the diagnosis, prognosis, genetic counseling and treatment options.
- If a diagnosis is suspected, schedule specific genetic testing.
- If there is no clinical suspicion, array CGH, metabolic testing and fragile X syndrome testing should be performed.
- If at this point diagnosis is still unknown, test for specific genes (ie MECP2 in girls with

GDD/ID, gene panels for X-linked mental retardation cases, etc).

- An abnormal neurological examination suggests the need for cerebral MRI.
- If imaging is normal, ancillary investigations are added and possibly establish a timetable for periodic reassessments, meanwhile ensuring the required services for the child and the family.

CONCLUSIONS

Developmental disorders, common presentations in pediatric and pediatric neurology wards, represent an extremely heterogeneous group and are major public health problems, involving multidisciplinary effort with diagnostic, educational and social services, with high costs involved. Accurately identifying the etiology offers the possibility of improving the quality of life of patients with GDD/DI, establishing proactive individualized management plans, with limiting of the associated complications and comorbidities, thereby improving prognosis.

We would like to thank the team of researchers from the laboratory of human genetics of the National Institute for Research and Development in the field of Pathology and Biomedical Sciences "Victor Babes", Bucharest, which made possible the testing and diagnosis of many of our young patients.

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