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Behavioral Phenotypes in Genetic Syndromes Associated with Intellectual Disability and Autism

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Abstract

Studies of psychological and genetic factors underlying behavioral phenotypes in autism and intellectual disability are relevant for clinical psychology and medical genetics. A behavioral phenotype refers to a set of cognitive, communicative and social behavior features specific to a particular syndrome. Most common genetic conditions, such as Down, Williams or FRAXA syndromes, demonstrate specific behaviors and psychological attributes. However, despite diagnostic significance of behavioral phenotypes in intellectual disability, complex studies of intelligence, psychomotor and speech development are rare in genetic diseases, and are generally associated with assessments of individual cases. In this work, we overview psychological features of genetic syndromes associated with autism and intellectual disability. Additionally, attempts at studying children with genetic syndromes, aimed at more effective interventions and therapeutic programs, are discussed.

Keywords: Behavioral phenotype; Intellectual disability; Autism; Genetic syndrome; Clinical psychology

Abbreviations: ASD: Autism spectrum disorder(s); Array CGH: Array Comparative Genomic Hybridization; ADHD: Attention Deficit Hyperactivity Disorder; FRAXA: Fragile X syndrome type A; ID: Intellectual Disability; SNP array: Single Nucleotide Polymorphism array; WGS: Whole Genome Sequencing; AAMR: American Association on Mental Retardation

Introduction

The prevalence of autism spectrum disorders (ASD) and intellectual disability (ID) is currently estimated as 1-1.5% and 1%, respectively [1,2]. Accordingly, these conditions are considered as the most common disorders associated with impaired brain functioning in children.

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Multidisciplinary studies of ID and ASD began relatively recently. The availability of psychometric methods allowed psychologists to assess these conditions since the beginning of the 20th century. The first genetic cause of syndromic ID was identified only in the 1950s representing trisomy of chromosome 21 resulting in Down syndrome. Later, it has been shown that at least 40-50% of ID/ASD cases account for genetic factors contributing to the etiology of these diseases [3,4]. Over the last decades, studying behavioral phenotypes has been growing increasingly important for clinical psychology and genetics.

Behavioral phenotypes are defined as typical features of behavior, personality, cognitive and communicative development, associated with a specific biological disorder [5]. At present, it is recommended to evaluate at least five different areas including intellectual development, speech, attention, social interaction and behavior [6].

Hallmarks of individual behavior can be important diagnostic markers -as important as the presence of developmental abnormalities. Here, we overview psychological studies of genetic syndromes associated with ID/ASD considering the perspectives in the light of developing more effective interventions and therapeutic programs.

Psychological aspects of Genetic Disorders

The progress in identifying genetic mechanisms of ID and ASD was largely ensured by the emergence of new molecular technologies. The detection of submicroscopic genomic variations (micro deletions/duplications, CNV, SNP) has revolutionized molecular diagnosis of genomic variations in idiopathic ID and autism [3,4,7,8]. However, mechanisms of many genetic conditions featuring ASD and ID remain largely obscure, especially in case of the non-syndromic forms. Habilitation and intervention programs for children with ID and ASD are usually conducted at psychological centers, where genomic background of a child's condition may be unfortunately or unintentionally ignored. Nevertheless, the lack of sufficient data on specific clinical and behavioral features of a certain genetic disease hinders correct applications of symptoms-based intervention programs.

Recent introduction of high-resolution genetic methods to healthcare serves as a probable reason for limited amount of research works focused on establishing behavioral phenotype of rare genetic conditions. Modern technologies (e.g. molecular karyotyping; NGS) are able to detect genome variations at molecular resolution (i.e. <5-10 bp), while classical technologies of diagnosing chromosome imbalances (e.g. "classical" cytogenetic analysis) have a significantly lower resolution (5-7 Mbp). Until recently, the latter technologies were essential for diagnosis of genetic diseases [4]. Additionally, degree of ID/ASD may underlie the lack of research in behavioral phenotypes of genetic syndromes, as well.

Currently, the psychological examinations are frequently made for individuals with a lack of expressive speech and troubled speech understanding, hyperactivity, difficulties with fine and gross motor skills and other features complicating psychological testing. However, severe degree of ID/ASD is still one of the key stumbling points for the psychological testing. In Russia, for example, children with severe and profound ID were not included in the educational system until 1993 [9], leading to the deficit of studies in this field. Qualified assistance and intervention should be based not only on child's weaknesses, but also rely on preserved abilities and strengths. The need for diagnosis and therapy of both ID and ASD starting from an early age is generally recognized [10]. It is noted that early intervention can improve the results of standardized intelligence tests and speech development in children with autism [11]. Reviewing early intervention studies showed that interventions are most effective at the age from 24 to 48 months [12]. A variety of psychological tests used in the studies of ID/ASD are intended at the evaluation of intelligence quotient, degree of autistic manifestations, adaptive behavior, memory, thinking, attention and speech. In context of genetic syndromes, the basic principles for conducting psychological studies are the same as those applicable to general population. However, types of applied tests should depend on the main features of the syndrome and specific difficulties of a particular area, as shown in Table 1.

Disease	Psychological test	Areas	References
Rett syndrome	The Rett Syndrome Behavior Questionnaire	Behavior, emotional response	[13]
	Cattell Infant Intelligence Scale	Cognition	[14]
Down syndrome	Stroop Type Task – Day/Night Version; Tower of London; Modified Card Sorting Test	Executive functions (planning, maintaining attention, switching)	[15]
Fragile X (type A, FRAXA) syndrome	Test of Everyday Attention for Children, adapted Simon spatial interference task	Executive functions	[16]
Williams syndrome	Raven's Colored Progressive Matrices	Intelligence, visual-spatialabilities	[17]
	Leiter International Performance Scale	Intelligence	[18]
Kleefstra syndrome	Mini PAS-ADD interview	General; identifies need for further assessment in case of mental problems; aimed at non-specialists	[19]
Lesch–Nyhan syndrome	American Association on Mental Retardation (AAMR) Adaptive Behavior Scale	Behavior	[20]
Prader-Willi syndrome	Autism Diagnostic Interview – Revised	Autistic manifestations	[21]
Klinefelter syndrome	The Amsterdam Neuropsychological Tasks	Neurocognitive profiles	[22]
	Child Behavior Checklist	Emotional and behavioral functioning	[22]
Often used in different genetic conditions	Developmental Behavior Checklist	Behavior	[23]
	Vineland Adaptive Scales	Adaptive behavior (communication, self-care skills, etc.)	[14,19]
	TheAutism Diagnostic Observation Schedule	Autistic features	[19,21]
	Wechsler Intelligence Scales	Intelligence, visual-spatialabilities	[17,22]
	Challenging Behavior Questionnaire; the Activity Questionnaire; the Repetitive Behavior Questionnaire; the Mood, Interest and Pleasure Questionnaire-Short Form; the Social Communication Questionnaire	Autistic features (mainly parental questionnaires)	[24]

Table 1: Psychological tests for assessing different areas of functioning in children with genetic syndromes associated with ASD and ID (most of the tests are for children irrespective to their condition focusing on specific areas of functioning).

Down syndrome

Characteristic features of Down syndrome (trisomy of chromosome 21) are speech and motor skills difficulties, while visual-spatial abilities remain relatively intact [25]. As compared to peers with severe ID, children with Down syndrome present with weaker motor skills manifesting as clumsiness, and increased joint flexibility. Stereoscopic object recognition is reported to be disturbed and is explained by the underdevelopment of the fine motor skills. Down syndrome is noted for a

significant discrepancy between active and passive vocabulary [26].

Rett syndrome

Classic Rett syndrome is a developmental disorder manifesting predominantly in girls at 6 -18 months, caused by mutations in *MECP2* gene (Xq28). The disease is featured by a regression of psychomotor and speech development, disturbed play and troubled skills acquisition at the first stage of the disease, followed by a loss of previously acquired speech and motor skills. One of the special Rett syndrome's attribute is a loss of purposeful hand movements and a presence of specific hand-rubbing stereotypic movements. The third disease stage is noted by improved interaction and eye contact, although any activity is short-term. Finally, motor difficulties become more severe and a complete loss of expressive speech is observed [26,28].

FRAXA syndrome

FRAXA syndrome (genetic cause: the expansion of CGG-repeats within the *FMR1* gene) is marked by a child's recurrent desire for comprehensive communication, autistic features being more "unstable" compared to "classical" autism. During decline periods, motor and speech stereotypic manifestations deteriorate; a child may cease to respond to speech. With age, affected individuals present with more motor stereotypic movements, speech is noted for echolalia [23].

Williams syndrome

The syndrome (genetic cause: chromosome 7q11.23 deletion) is characterized by a hoarse voice and an absence of social fear. Patients with Williams syndrome typically present with a weak visuo-spatial integration which results in seeing individual components of a picture instead of perceiving it as whole. Many of them can play musical instruments, are sociable, have no delay in speech development [29].

Angelman syndrome

An overly positive mood, constant smile and inappropriate laughter are major hallmarks of Angelman syndrome, a genomic imprinting disorder caused by a variety of genetic/epigenetic abnormalities at chromosome 15q11q13 region. Children are interested in social interactions; many patients seek communication despite pronounced speech disorders. However, individuals with this syndrome experience difficulties in social interactions due to poor understanding of social and emotional clues [30].

Prader-Willi syndrome

Behavioral phenotype in Prader-Willi syndrome (another genomic imprinting disorder caused by a variety of genetic/epigenetic abnormalities at chromosome 15q11q13 region) manifests as mood swings, persistence, manipulative behavior, obsessive-compulsive disorder and difficulty in routine change. The syndrome is also associated with an increased risk of psychiatric disorders. Patients with a uniparental disomy are more prone to psychosis than those with a deletion [23]. The temper tantrums and physical aggression are shown to persist past teenage years and experience certain decline after 19 years contrary to some other genetic disorders (e.g. Down and FRAXA syndromes show temper tantrums' decline prior to adulthood) [31].

1p36 deletion syndrome

Motor development delay is the most commonly noted feature of this syndrome. About 25% of patients gain independent walking skill, with a wide gait, at about 2-7 years. Expressive speech is absent in 75% of cases, receptive speech is contextual. Communication is weak but improves with age and with extension of the gesture repertoire [32].

Klinefelter syndrome

Children with Klinefelter syndrome (genetic cause: additional chromosome X in males) commonly present with weak emotional skills and immaturity. They have been noted for excessive suggestibility, imitation, lack of independence, excessive attachment to relatives. The mood is usually elevated with unreasonable fluctuations sometimes leading to affective outbreaks [33].

Turner syndrome

Although intellectual disability is not typical for Turner syndrome (genetic cause: functional monosomy of the chromosome X short arm or mosaic/nonmosaic chromosome X loss), apart from cases caused by ring chromosome X, researches highlight learning difficulties, troubles with spatial perception and motor control. Various studies empathize problems with visual-spatial coordination, executive functions (speech fluency, planning skills, etc.), memory and attention. Infantilism has also been described in patients [34].

Kleefstra syndrome

Contrast to most syndromes characterized by a regression in functioning, a Kleefstra syndrome (genetic cause: chromosome 9q34.3 micro deletion) is featured by sudden decline during adolescence,

but not childhood. Patients suffering from regression score high for psychosis. Patients are prone to obsessive-compulsive disorder and depressive episodes [35].

Smith-Magenis syndrome

Eighty percent of patients with Smith-Magenis syndrome (genetic cause: haploinsufficiency of *RAI1* gene located on chromosome 17p11.2) exhibit self-mutilation (auto aggression), including onychotillomania, wrist biting, head shaking, increased tolerance to pain and sleep disturbance. Autism has been described in at least 4 patients with a chromosome 17p11.2 deletion. Receptive speech skills are more advanced than expressive ones. A hoarse voice features the syndrome. The use of sign language greatly improves the communicative abilities [36].

The Cri-du-chat syndrome

In Cri-du-chat syndrome (genetic cause: deletions at the short arm of chromosome 5), the greatest developmental delay is observed for skills that require mobility, dexterity and verbal communication. Gross motor skills are more advanced than fine ones: children are able to wave or catch a rolling ball. Lack of speech is compensated for about 2/3 of children by non-verbal methods of communication; about 50% of children are able to use sign language to communicate basic needs [37]. The main features of common genetic syndromes are presented in Table 2.

Disorder	Incidence	Intellectual disability	Autism	Features and main troubled areas
Down syndrome	1:650-850	Moderate to severe (IQ = 25-55)	Autistic features are noted in some cases	Speech, motor skills, working memory, executive functions [26,38]
Rett syndrome	1:10000 (in girls)	Severe	Autistic features	Fine motor skills, speech, stereotypic movements [13,14,27]
FRAXA syndrome	1:3600 – 1:4000 in boys and 1:4000 - 1:6000 in girls	From borderline (IQ = 70) to severe. Most often mild or moderate.	Autistic features	Specific speech, executive functions, short-term memory, visual-spatial memory, ADHD (attention deficit hyperactivity disorder) [39]
Williams syndrome	1:7500 to 1 : 20000	Moderate (IQ 58-69)	No	Motor skills, speech, anxiety, ADHD [18,40]
Angelman syndrome	1:12000	Severe	Autistic features	Speech, gait coordination, hyperactivity, attention, impulsivity [30]
Prader-Willi syndrome	1:15000	Moderate (average IQ - 60)	ASD	Dyslexia, rituals in behavior, compulsive symptoms [31]
1p36 deletion syndrome	1:5000 – 1:10000	Severe	Not mentioned	Speech, interaction, sudden mood changes, self-mutilation, stereotypic behavior [32]
Klinefelter syndrome	1:500 – 1:1000	Mild to normal intelligence	No	Executive functions, attention, perception, memory and abstract thinking, dyslexia [33]
Turner syndrome	1:2000- 1:5000	Mild to normal intelligence	No	ADHD, visual and spatial and executive functions [41]
Kleefstra syndrome	Unknown (114 cases have been described)	Moderate to profound	Autistic features	Vulnerable to severe psychiatric disorders (psycholsis, depressive mood disorder) [35]
Potocki-Lupski syndrome (17p11.2 duplication)	1:25,000	Varies	ASD	Repetitive behaviors, anxiety, hyperactivity [24]
Smith-Magenis syndrome	1:25000	From mild to severe	Variable	Behavioral difficulties, aggression, sudden mood changes, attention deficit, upper body hugging. [36]
Cri du chat syndrome	1:50000	Moderate to severe	Autistic features	Behavioral difficulties, repetitive behavior, hypersensitivity [37]

Table 2: The main features of common genetic syndromes.

Conclusion

Currently, the literature dedicated to behavioral phenotypes of genetic syndromes mainly describes frequent conditions, while less common diseases remain poorly described from a psychological point of view. Numerous genetic diseases remain an actual focus of psychological research, in as much as frequently presenting with multiple cognitive, motor and behavioral disorders, as well as difficulties in social interactions and communication [42]. Although there are special assessment tests and intervention programs for the most common genetic syndromes, rare conditions still require thorough multidisciplinary research [43,44]. Typical behavioral phenotypes, natural limitations and opportunities for psychological studies should be considered while developing psychological methodologies for a certain genetic condition [45]. Today, an important task is the creation of approaches to the psychological research of children with genetic neuropsychiatric disorders. We believe that these achievements will contribute to full understanding of various areas of a child's functioning and will allow the development of disease-targeted questionnaires for the psychological examination.

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