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ORIGINAL ARTICLE

Children and adolescents with intellectual disabilities studied with genetic tests according to their clinical phenotype

Estudio genético de acuerdo a características fenotípicas de niños y adolescentes con discapacidad intelectual de etiología indeterminada

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What do we know about the subject matter of this study?

Intellectual disability is a neurodevelopmental disorder that affects intellectual functioning and adaptive capacity, including conceptual, social, and practical skills, affecting 1-3% of the world's population. It has multiple etiologies, and the approach can be complex. There is a group of patients with undetermined etiology that is probably genetic.

What does this study contribute to what is already known?

This study presents clinical aspects and evaluations of cognitive functioning of a group of children and adolescents with a diagnosis of intellectual disability of undetermined cause, approaching the study with genetic panels and chromosomal microarray tests according to the phenotypic characteristics of the patients.

Abstract

Intellectual disability (ID) is a neurodevelopmental disorder characterized by limitations in intellectual and adaptive functioning, of various etiologies, including genetic causes. **Objective:** to describe genetic studies carried out in a series of children and adolescents with ID of previously undetermined etiology, considering their phenotypic characteristics. **Patients and Method:** Descriptive study of a series of patients with ID aged 6 to 18 years. Clinical records, cognitive assessment results (Wechsler -TADI), and genetic study performed were reviewed. They were classified according to phenotypic characteristics into Group 1 patients without a specific phenotype, Group 2: patients with Angelman- and Rett-like neurodevelopmental disorders phenotype, and Group 3: patients with difficult-to-control seizures. Group 1 was studied with CMA and Groups 2 and 3 with specific genetic panels.

Keywords:
Intellectual Disability;
Neurodevelopment;
Psychomotor Development;
Genetic Testing Panels

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Results: 18 patients were described, average age 11 years, male predominance, non-consanguineous parents, and with history of psychomotor retardation. Common comorbidities were epilepsy, autism spectrum disorder (ASD), and behavioral difficulties. Most had a neurological examination without focus and had TADI with very poor developmental ages. In Group 1, there was one patient with a 16p11.2 microdeletion and in Group 3 a duplication of the IQSEC2 gene was found in a patient with difficult-to-control seizures. **Conclusions:** The phenotypic characteristics allow to guide the choice of specific genetic studies in children and adolescents with ID of previously undetermined etiology to approach the etiological diagnosis.

Introduction

Intellectual disability (ID) is a developmental disorder that affects adaptive behavior in the conceptual, social, and practical domains, along with limitations in intellectual functioning that is significantly below average, confirmed by clinical assessment and standardized tests[1-5].

From early childhood, people with ID present with psychomotor developmental delay (PMDD) in isolation or associated with other neurological conditions such as epilepsy and autism spectrum disorder (ASD). Despite advances in finding the cause, the etiology is still not identified in an important group of patients. The etiology of ID is varied, and genetic causes are estimated in 50% of patients, identifying more than 700 genes associated with different types of inheritance[6-9].

The development of new techniques for genetic studies has increased the diagnostic performance in patients with ID[10,11]. The new generation of studies includes the development of genetic panels, which have been useful in directing the study to specific pathologies, and the chromosomal microarray (CMA), which in cases of ID detects 15 to 30% variations in the number of copies (microdeletions, microduplications)[12,13]. This, along with whole-exome and genomic sequencing techniques, has contributed to the detections of new genetic causes and has broadened the phenotypic spectrum of genetic disorders with known etiology[14-16].

The objective of this study was to describe the results of genetic studies carried out in a series of children and adolescents with intellectual disabilities of previously undetermined etiology, considering their phenotypic characteristics.

Patients and Method

Descriptive study. We included children and adolescents with a diagnosis of ID who had undergone a previous etiological study with no identifiable cause, classifying them as cases of ID of undetermined etiology. The study was carried out with patients aged between 6 to 18 years evaluated between January 2018 and January 2020, by the team of the Child Neuropsychiatry Service of the *Hospital Clínico San Borja Arriarán* (HCSBA), Santiago, Chile. Face-to-face clinical evaluations and review of clinical records were carried out, recording sex, age, family history of ID and consanguinity, personal history of PMDD, epilepsy, ASD, behavioral difficulties, stereotypies, current neurological examination, and previously performed studies.

To approach the study, the patients were subdivided into 3 groups according to their phenotypic characteristics, which allowed a targeted description and selection of the genetic study (figure 1).

Group 1

ID patients without a specific phenotype. In this group, the clinical examination, evaluations, and diagnostic tests do not show etiological indicators of the cause of ID, and they do not present special phenotypic characteristics. They were studied with CMA, which is used as a first-line study in ID[13].

Group 2

Patients with ID associated with a phenotype of neurodevelopmental disorders with clinical characteristics of Angelman/Rett-like syndrome. In this group, there were patients with clinical features suggestive of Angelman Syndrome and/or Rett Syndrome, highlighting in their clinical phenotype microcephaly, epilepsy, and stereotypies. Patients who did not meet all the diagnostic criteria to classify them as Angelman and/or Rett syndrome, or have etiological studies that rule out these pathologies, were defined as Angelman/Rett-like syndrome.

Group 3

Patients with ID and refractory epilepsy. In this group, epilepsy that has been treated with more than 3 antiepileptic drugs stands out in its phenotype. Structural causes had been ruled out with neuroimaging and previous studies that have not determined the etiology of ID.

For Groups 2 and 3, it was determined to use specific commercial gene panels designed for the study of patients with neurodevelopmental disorders or epilepsy.

As part of this study, intellectual functioning evaluations were updated for patients with evaluations older than one year, using standardized instruments for the Chilean population. The Wechsler Intelligence Scale for Children fifth edition (WISC-V) was used for children between 6 and 16 years old and the Wechsler Adult Intelligence Scale fourth edition (WAIS-IV) for patients aged 16 years and older. Total IQ (TIQ), composite scores (CS), and qualitative scores (QS) were recorded.

In patients with clinical severity that could not be evaluated with the Wechsler scale to obtain intellectual functioning, the evaluation was performed with the Child Learning and Development Test (TADI) allowing to obtain developmental ages[17]. This instrument evaluates development between 3 months and 6 years of age regarding cognition, language, motor, and socioemotional dimensions. Raw scores and age ranges were reported for the activities that the patient was able to perform in the age ranges achieved in each dimension. The study considers the cognition dimension and its developmental age ranges. This test was applied as an adapted instrument.

The genetic study was scheduled according to the group in which each patient was classified. Group 1 patients were studied with CMA (CentoArray Cyto™ - 750 K) that allows detection of copy number variations (CNV) and/or large deletions/duplications. CNVs with a minimum of 25 markers and size > 50 kb (deletions) and 200 kb (duplications) were reported. Group 2 was studied with Rett/Angelman syndrome and related disorders gene panel including 28 genes, and Group 3 was studied with epilepsy gene panel including 187 genes. Genetic panels were performed with sequencing and gene deletion/duplication analysis (Illumina technology). The analyses were performed in a certified genetic diagnostic laboratory.

This study was approved by the Scientific Ethical Committee of the Central Metropolitan Health Service, with the informed consent of the participants' parents.

Results

Eighteen children and adolescents with ID of previously undetermined etiology were evaluated. The results are described in each group as follows:

Group 1: Patients with ID without specific phenotype

Nine patients between 6 and 18 years of age were studied (mean 12 years), predominantly male. In clinical history, all patients had non-consanguineous parents and the mother of one patient had history of ID.

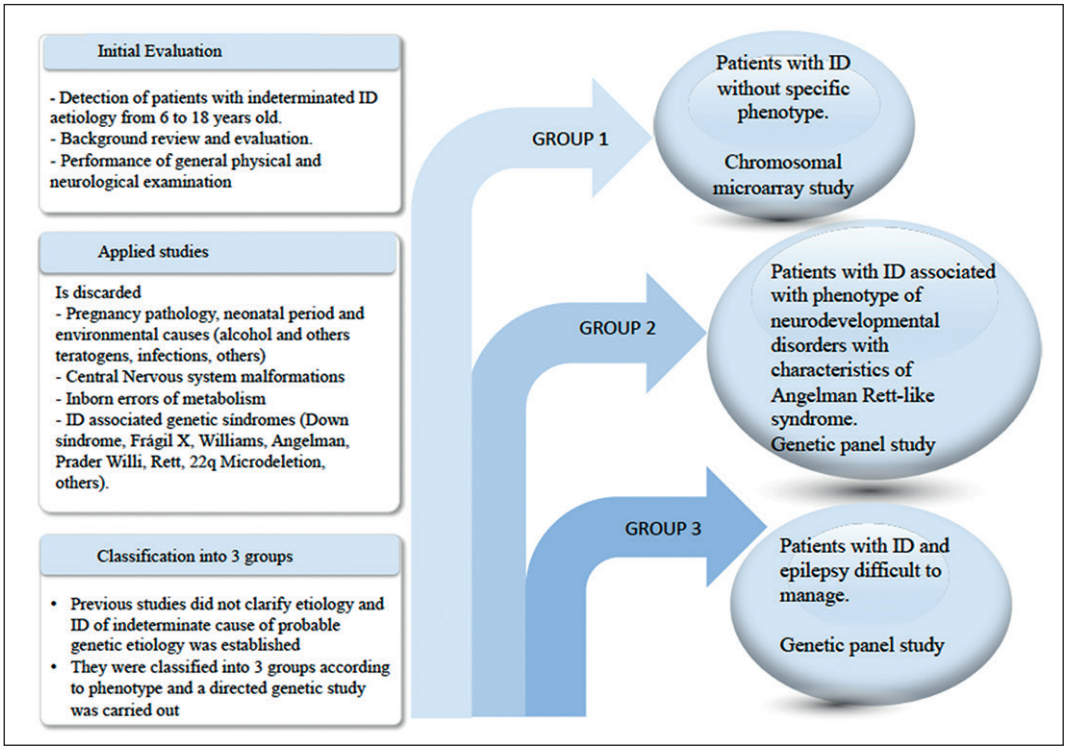

Figure 1. Referral algorithm and study of patients with Intelectual Disabilities (ID).

All patients presented with PMDD, in most of them it was global. Neurological comorbidity with non-refractory epilepsy was present in 4 patients, 3 patients with ASD features, and 6 patients with behavioral difficulties. In the neurological examination, most of them were normocephalic, without pyramidal, extrapyramidal, or cerebellar involvement. The Weschler scale was applied to 4 patients and the TADI to 5 patients.

The CMA showed a pathogenic result, detecting a 16p11.2 microdeletion in a 6-year-old male patient with history of global PMDD, who presented severe ID, non-refractory epilepsy, autistic spectrum features, behavioral disorder, and history of ID on the mother's side. The patient was evaluated with the TADI, determining a developmental age between 30 and 36 months (patient nº 5).

In one patient, a CNV was found in the 11p12 region, of uncertain significance and one patient was a carrier of a 16q24.3 heterozygous deletion which was classified as pathogenic CNV. The other 6 patients presented negative results (table 1).

Group 2: Patients with ID associated with a phenotype of neurodevelopmental disorders with characteristics of Angelman/Rett-like Syndrome

We studied 3 patients aged 7 to 15 years (mean 11 years), all female, with microcephaly and midline stereotypies. In the clinical history, all of them had non-

Table 1. Description of Group 1: Clinical characteristics and result of genetic study with chromosomal microarray in patients with intellectual disability without specific phenotype

	Patient Number								
	1	2	3	4	5	6	7	8	9
Age (years)	16	10	10	8	6	8	18	17	18
Gender	M	M	M	M	M	M	F	F	M
ID Family history	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)
Consanguinity	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
PMDD	(+)G	(+)G	(+)G	(+)MP	(+)G	(+)G	(+)G	(+)G	(+)LP
Epilepsy	(-)	(+)	(-)	(-)	(+)	(-)	(+)	(-)	(+)
Behavioral Difficulties	(+)	(+)	(+)	(-)	(+)	(-)	(+)	(-)	(+)
ASD	(+)	(-)	(+)	(-)	(+)	(-)	(-)	(-)	(-)
Midline Stereotypy	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)
Microcephaly/Macrocephaly	Macro cephaly	(-)	(-)	(-)	(-)	(-)	Micro cephaly	(-)	Macro cephaly
Pyramidal syndrome	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Extrapyramidal syndrome	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Cerebellar syndrome	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Wechsler cognitive study (WISC V)	WISC-V TIQ CS 45 / EL	-	-	-	-	WISC-V TIQ CS 54 / EL	-	WISC-V TIQ CS 40 / EL	WAIS-IV TIQ 55 / VL
TADI (month) cognitive study	-	18 to 24	9 to 12	30 to 36	30 to 36	-	18 to 24	-	-
Genetic study	Carrier	(-)	(-)	(-)	(+)	(-)	(-)	Inc	(-)
Variant	16 q 24.3 Deletion	(-)	(-)	(-)	16p11.2 Micro-deletion	(-)	(-)	11 p12 region duplication	(-)
Variant clasification	CNV pathogenic	(-)	(-)	(-)	CNV pathogenic	(-)	(-)	VUS	(-)

M: male, F: female, (-): negative, (+): positive, PMDD: psychomotor developmental delay, G: global, MP: motor predominance, LP: language predominance, ASD: autism spectrum disorder, TADI: values of age of development-dimension cognition in months, WISC-V: TIQ: Total Intelligence quotient, CS: composite score, Qualitative score: EL: extremely low, VL: very low. U: uncertain, CNV: copy number variant, VUS: variant of uncertain meaning.

consanguineous parents and had no family history of ID. All patients presented global PMDD. One patient had non-refractory epilepsy and another one presented behavioral difficulties. Only one patient had dystonia. All 3 patients were evaluated with the TADI.

They were studied with a genetic panel for Rett/Angelman syndrome and related disorders, with one patient presenting a result of uncertain significance and 2 patients with a negative study (table 2).

Group 3: Patients with ID and refractory epilepsy

We studied 6 patients with ID and refractory epilepsy, aged between 6 and 14 years (mean 10 years), predominantly male. None of them had history of consanguineous parents or ID in the family. All patients presented with PMDD, mostly global. Two patients had behavioral difficulties and one patient had ASD features. On the clinical examination, one patient presented microcephaly and one patient pyramidal involvement. Four patients were evaluated with the TADI and two with the Weschler scale.

In a 10-year-old male patient presenting with global PMDD, severe ID, ASD, behavioral difficulties, epilepsy, and microcephaly, the genetic analysis with the epilepsy panel showed a pathogenic result (IQSEC2 gene duplication). The patient was evaluated with the TADI and was classified in the cognition dimension in the age range between 3 to 6 months (patient nº 13). In the other 5 patients, no specific etiology was found with the study performed, specifically, 2 patients were carriers of heterozygous pathogenic variants and 3 patients with variants of uncertain significance (table 3).

Discussion

We studied children and adolescents with ID of undetermined etiology, probably of genetic origin. Most of them presented history of global PMDD and associated neurological conditions, most frequently epilepsy and features of ASD. In the series, most of the patients had severe clinical involvement, and the TADI

Table 2. Description of Group 2: Clinical characteristics and study result with Rett/Angelman syndrome genetic panel and related disorders in patient with intelectual disability

	Nº Paciente		
	10	11	12
Age (years)	15	7	12
Gender	F	F	F
ID Family history	(-)	(-)	(-)
Consanguinity	(-)	(-)	(-)
PMDD	(+) G	(+) G	(+) G
Epilepsy	(+)	(-)	(-)
Behavioral Difficulties	(-)	(-)	(+)
Autism Spectrum Disorder	(-)	(-)	(-)
Midline Stereotypy	(+)	(+)	(+)
Microcephaly	(+)	(+)	(+)
Pyramidal syndrome	(-)	(-)	(-)
Extrapyramidal syndrome	(+)	(-)	(-)
Cerebellar Syndrome	(-)	(-)	(-)
Cognitive study TADI (month)	30 to 36	54 to 60	6 to 9
Genetic study	Uncertain	(-)	(-)
Gene	GABRD / MEF2C	(-)	(-)
Variant	Deletion (entire coding sequence) / c.1021G>A p.Ala341Thr	(-)	(-)
Zygocity	Heterozygous	(-)	(-)
Variant Clasification	VUS	(-)	(-)

M: male, F: female, (-): negative, (+): positive, PMDD: psychomotor developmental delay, G: global, TADI: values of age of development-dimension cognition in months, U: uncertain VUS: variant of uncertain meaning.

Table 3. Description of Group 3: Clinical characteristics and study result with epilepsy genetic panel in patient with intelectual disability

	Patient Number					
	13	14	15	16	17	18
Age (years)	10	13	11	14	7	6
Gender	M	M	M	F	M	F
ID Family history	(-)	(-)	(-)	(-)	(-)	(-)
Consanguinity	(-)	(-)	(-)	(-)	(-)	(-)
PMDD	(+) G	(+) G	(+) MP	(+) LP	(+) G	(+) G
Epilepsy	(+) DM	(+) DM	(+) DM	(+) DM	(+) DM	(+) DM
Behavioral Difficulties	(+)	(-)	(+)	(-)	(-)	(-)
Autism Spectrum Disorder	(+)	(-)	(-)	(-)	(-)	(-)
Midline Stereotypy	(-)	(-)	(-)	(-)	(-)	(-)
Microcephaly	(+)	(-)	(-)	(-)	(-)	(-)
Pyramidal syndrome	(-)	(+)	(-)	(-)	(-)	(-)
Extrapyramidal syndrome	(-)	(-)	(-)	(-)	(-)	(-)
Cerebellar syndrome	(-)	(-)	(-)	(-)	(-)	(-)
Wechsler cognitive study (WISC V)	-	-	-	WISC-V TIQ CS: 59 / EL	WISC-III Mild ID	-
Cognitive study TADI (month)	3 to 6	9 to 12	6 to 9	-	-	30 to 36
Genetic study	(+)	Carrier	Uncertain	Carrier	Uncertain	Uncertain
Gene	IQSEC2	PIGG	SETD2	TPP1	GRLA1	REL / REL
Variant	c.4402_4418dup (p.Ser1474 Alafs*27)	Deletion (entire coding sequence)	c.1664A>C (p.Tyr555Ser)	c.1424C>T (p.Ser475Leu)	c.31C>A (p.Leu11Ile)	c.2725G>A (p.Ala909Thr)/ c.7043G>A (p.Gly2348Asp)
Zygocity	Homozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous
Variant Clasification	CNV pathogenic	CNV pathogenic	VUS	CNV pathogenic	VUS	VUS

M: male, F: female, (-): negative, (+): positive, PMDD: psychomotor developmental delay G: global, MP: motor predominance, LP: language predominance, DM: difficult to manage, WISC-V: TIQ: Total Intelligence quotient, CS: composite score, QR: qualitative rating, EL: extremely low, TADI: values of age of development-dimension cognition in months, U: uncertain, CNV: copy number variation. VUS: variant of uncertain meaning.

adapted as a tool to determine developmental ages was applied to a large part of the group[17,18].

As a result of the studies performed, a genetic origin of ID was found in only 2 patients, one patient with a 16p11.2 microdeletion of autosomal dominant inheritance detected with CMA and one patient with a duplication in the IQSEC2 gene detected in the epilepsy panel.

In the phenotype of the 16p11.2 microdeletion syndrome, PMDD, ID and/or ASD, epilepsy, microcephaly, and obesity have been described; it has autosomal dominant inheritance and usually occurs *de novo* but up to 20% can be inherited[19-21]. IQSEC2-related disorders represent phenotypes characterized by ID as the main feature with X-linked inheritance. In the spectrum of clinical features, it has been described in syndromic and non-syndromic ID and in patients with severe ID and epilepsy, who may present strabismus, hypotonia, and ASD features[22].

In the series, we detected patients with heterozygous pathogenic variants and variants of uncertain significance, most of them occurred in patients of

Group 3 (2 with heterozygous pathogenic variants and 3 of uncertain significance). It is not possible to give diagnostic value to this information and it is necessary to follow up on the updates of the databases over time and carry out studies focused on the parents since these variants may be reclassified[23].

In our experience, the initial approach of the diagnostic algorithm and the classification of patients into the 3 groups described allowed us to guide the choice of the genetic study according to clinical characteristics of patients with ID. Specifically, in the choice of Groups 2 and 3, it was considered that both neurodevelopmental disorders such as Angelman/Rett-like syndrome and refractory epilepsy are frequent phenotypes in patients with ID, therefore, we believe it is useful to first study the most frequent genes found in this type of conditions, which are included in the respective panels as a first approach to the etiological diagnosis from the clinical phenotype.

Further studies are needed to increase the number of children and adolescents to be evaluated, also considering the use of new-generation tests such as exome and/or genomic analysis that improve diagnostic performance. As a disadvantage, the latter, as well as the tests performed in this study, are expensive and are not implemented in the public health system, thus, it is even more necessary to optimize the genetic studies available.

Finding the etiology in ID allows the clinician to detect comorbidities, guide the patient's specific management and treatments, and provide genetic counseling. Families who have known the cause of ID highlight that the diagnosis allowed them to know their child's condition better and to obtain specific support. In addition to knowing the cause, it is a challenge to deepen the knowledge of the adaptive behavior and quality of life areas in patients with ID.

Conclusion

This clinical series describes clinical aspects, cognitive evaluations, and results of specific genetic studies chosen according to the clinical phenotype of children and adolescents with ID of previously undetermined etiology, detecting the genetic cause of ID in 2 patients. It is useful to approach the genetic study according to the presence of phenotypic characteristics associated with ID, which allows us to guide the study and rationalize the resources that are currently limited in our public health system. Knowing the cause of ID allows the family to have a better knowledge of the patient's condition and the health team to carry out the management, follow-up, and pertinent adaptations on a case-by-case basis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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