Aetiological evaluation of mental retardation in Brazilian patients

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INTRODUCTION: Mental retardation is present in approximately 2-3 % of the population. Clinical geneticists are frequently asked to evaluate children with development delay or mental retardation. Identifying the cause of the mental retardation will benefit individuals and families, answering questions about management, prognosis, recurrence risks and prevention.

MATERIAL AND METHODS: A genetic diagnostic survey in a population of 260 mentally retarded institutionalized patients in the South of Brazil is presented.

RESULTS: The patients had a male:female ratio of 1.3:1 and their ages varied from 1 month to 47 years with a mean of 5 years and one month. Using personal and family data, careful clinical examination and laboratory investigation, the authors established a definitive diagnosis in 171 patients (65.76%). A constitutional disorder was present in 147 patients (56.53%).

CONCLUSION: Down syndrome patients represented 32.30% and 3,84% had other chromosomal anomalies, including microdeletion syndromes. In 32 patients (12.30%) a mendelian inheritance disorder was diagnosed. In eleven patients (4.23%) a MCA/MR syndrome was recorded. Ten patients (3.84%) presented a CNS malformation. An acquired condition was observed in 26 patients (10%), representing 7.69 % of CNS dysfunction, 2.3% of pre- or postnatal infection and 0.4% of postnatally acquired conditions other than infections. In the remaining 87 patients (34.46%) a conclusive diagnosis was not possible.

Key-words: Genetics of mental retardation; etiologia, MCA/MR syndromes, syndromes.

Avaliação etiológica da deficiência mental em pacientes brasileiros

INTRODUÇÃO: Retardo mental está presente em aproximadamente 2-3% da população. Geneticistas clínicos são chamados freqüentemente para avaliar crianças com atraso no de senvolvimento neuropsicomotor ou deficiência mental. A identificação da causa da deficiência mental irá beneficiar o indivíduo e famílias, respondendo questões sobre manejo, prognóstico, risco de recorrência e prevenção.

MATERIAL E MÉTODOS: Análise genético-clínica numa população de 260 deficientes men tais de uma instituição é apresentada.

RESULTADOS: Os 260 pacientes distribuíram-se numa razão de 1.3 do sexo masculino para 1 do sexo feminino. A idade variou de 1 mês a 47 anos com a mediana de 5 anos e um mês. Usando dados pessoais e familiares, exame físico detalhado e investigação laboratorial, os autores estabeleceram diagnóstico definitivo em 171 pacientes (65,76%). Alterações constitucionais estavam presentes em 147 pacientes (56,53%).

CONCLUSÃO: Pacientes com Síndrome de Down representaram 32,20% e 3,84%

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apresentaram anomalias envolvendo outros cromossomos, incluindo síndromes de microdeleção. Em 32 pacientes (12,30%) uma doença mendeliana foi diagnosticada. Em 11 pacientes (4,23%) uma anomalia congênita múltipla/retardo mental (ACM/RM) foi diagnosticada. Dez pacientes (3,84%) apresentaram uma malformação do sistema nervoso central (SNC). Uma condição adquirida foi observada em 26 pacientes (10%), representando 7,69% de disfunção do SNC, 2,3% de infecção pre ou pós-natal e 0,4% de dano pós-natal, excluindo infecções. Em 87 pacientes (34,46%) não foi possível determinar um diagnóstico.

Unitermos: Genética da deficiência mental; etiologia; síndromes de ACM/RM; síndromes.

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Introduction

Mental retardation (MR) is present in approximately 2-3% of the population in industrialized countries. The prevalence of severe mental retardation was estimated as 3-5.8/1000 in Europe and the United States of America (1). In developing countries the prevalence is higher. In Pakistan the incidence of severe mental retardation was reported as 11/1000 live births (2). In Brazil, it had been estimated as 6.7/1000 (3).

Clinical geneticists are frequently asked to evaluate children with development delay or mental retardation. Identifying the cause of the mental retardation will benefit individuals and families, answering questions about management, prognosis, recurrence risks and prevention (4).

The causes of MR have been studied mainly in developed countries. Several diagnostic-genetic surveys of institutes for mentally retarded have been published specially in Belgium, Dutch and American institutions (5-12).

Until 1998 there was no similar studies in Brazil. In 1998 the authors reported a diagnostic survey in 202 patients in an institution for mentally retarded individuals in the south of Brazil (13). In the present study the authors report an update of the previous study.

Material and methods

During the period from 1989 to 2001, 260 mentally retarded patients were evaluated at the Medical Genetics Service of the Hospital de Clínicas de Porto Alegre, in the south of Brazil. All these patients were from an institution for mentally retarded individuals, the Associação dos Pais e Amigos dos Excepcionais (APAE), located in Caxias do Sul, 122 km far from Porto Alegre. Caxias do Sul is an industrial city of 360 thousand inhabitants, mainly of Italian origin. The institution was founded in 1957 and functions as a reference for the assistance of mentally retarded. It includes an early intervention program with stimulation in motor function, cognitive and language development, special education and professional training. The majority of the individuals (238 patients) were severely mentally retarded. Twenty-one were ascertained as mild mentally retarded and in one patient the degree of mentally handicap could not be established. Their ages varied between 1 month and 47 years, with a mean of 5 years and one month. The male:female ratio was 1.3:1.

Personal and medical histories were recorded, and clinical examination was performed with special attention to dysmorphology in all patients (4).

Chromosomal analysis was performed in all patients. FISH studies were performed when a microdeletion syndrome was suspected. Metabolic screening was chosen based on the presence of suggestive clinical and physical findings. Additional technical examination such as X-ray skeletal survey, computerized axial tomography, magnetic resonance imaging, electroencephalography and electromyography were performed which were necessary to contribute to a more precise diagnosis.

The classification used for etiological factors in this mentally retarded population was the same proposed in Belgian reports (7). This was used to classify patients into 5 main categories: constitutional disorders (chromosomal anomalies, mendelian inheritance

disorders, multiple congenital anomalies/mental retardation (MCA/MR) syndromes and CNS malformations); acquired CNS dysfunction due to pre, peri and postnatal origin; patients with pre- or postnatal infection; postnatal acquired conditions and non-classified conditions.

Results

Constitutional Disorders

In 147 patients (56.53%) a constitutional disorder was found to be the cause of mental retardation.

1. Chromosomal anomalies: In 94 patients a chromosomal anomaly was detected. Eighty four patients had Down syndrome. The karyotype was performed on 79 patients. In 73 patients a regular trisomy 21 was detected, three showed a mosaic constitution and three an unbalanced translocation. The mean maternal age for 73 patients with regular trisomy 21 was 33.59 years (SD= 7.9). Of the other 5 patients, a marker chromosome was detected in two, a partial duplication for chromosomes 8 and 10 in two and a deletion of the short arm of chromosome 18 in the remaining (table 1). In 5 patients a microdeletion syndrome was diagnosed by molecular cytogenetics analysis. A paternal 22q11.2 deletion was detected in the Velocardiofacial syndrome patient by FISH and molecular analysis. A paternal 7q11.23 deletion that includes the ELN gene was diagnosed by molecular analysis in one Williams syndrome patient. A maternal 15 q deletion was diagnosis in three patients with Angelman syndrome (table 2);

2. Mendelian disorders: In 32 patients a mendelian inherited mental retardation syndrome was detected. In table 3 they were listed according to the number in McKusick´s catalogue (14). The achondroplasia patient had hydrocephalus and mental retardation. The hypothyroidism patient was born from consanguineous parents. The mother and brother from the child with autosomal dominant microcephaly were also affected. Fragile X syndrome was diagnosed by molecular studies. Four patients with X linked mental retardation were fragile X negative by molecular analysis;

Table 1. Chromosomal anomalies[a]

Abnormality	n
Down syndrome	84
47,+21	73
47,XX +21/46,XX or 47,XY +21/46,XY	3
46,XX der(14;21)	1
46,XX der(21;21)	1
46, XX der (21;22)	1
without karyotype	5
Others	5
47,XY, +mar	2
46,XX, 8p+	1
46,XX, 10q+	1
46,XX, 18p-	1

[a] n = 89.

3. Malformation syndromes: Eleven patients with multiple congenital anomalies and mental retardation with unknown transmission were recorded (table 4);

4. CNS malformation: The central nervous system malformations detected in 10 patients are listed in table 5.

Central nervous system dysfunction of prenatal, perinatal or postnatal origin (except infections)

A well-delineated prenatal, perinatal or postnatal cause was recorded in 20 patients (7.69%), as listed in table 6. In two, complications

Table 2. Microdeletion syndromes[a]

Syndrome	n
Angelman	3
Williams	1
Velo cardio facial	1

[a] n = 5

Table 3. Mendelian disorders[a]

McKusick´s number	Syndrome	n
Autosomal Dominant		10
191100	Tuberous sclerosis	2
122470	Cornelia De Lange syndrome	2
160900	Myotonic Dystrophy	1
101200	Apert syndrome	1
100800	Achondroplasia	1
12940	Rapp-Hodgkin syndrome	1
156580	Microcephaly	1
	Familial macrocephaly	1
Autosomal Recessive		5
230400	Galactosemia	1
249800	Metachromatic leucodystrophy	1
251200	Microcephaly	2
210600	Seckel syndrome	1
-	Hypothyroidism	1
X-linked		17
309550	Fragile X syndrome	9
304100	Agenesis of corpus callosum	2
309000	Lowe oculocerebrorenal syndrome	1
305100	Ectodermal dysplasia hypohidrotic	1
-	X- linked mental retardation	4

[a] n = 32.

secondary to prematurity were recorded. One patient was born with 31 weeks of gestation and evolved with severe perinatal complications. Six children were delivered from twin pregnancies. In two out of the 6 twins, the other twin was a stillbirth.

Pre or postnatal infections

Five patients (2.30%) with well-defined pre- or postnatal infections are listed in table 7. The cause of prenatal infection was only established in one patient with congenital toxoplasmosis. In two patients (TORCH infection), 3 and 4 years-old respectively, multiple periventricular calcifications were observed on CT scan. Both had normal eye examination and conclusive ORCH 1ters, as these exams were not performed at birth.

Postnatally acquired conditions

One patient (0.4%) was diagnosed as mentally retarded with cranio-encephalic trauma, after a car accident.

Table 4. Malformation (MCA/MR) syndromes with unknown transmission[a]

Mckusick´s number	Syndrome	n
130650	Beckwith-Wiedemann syndrome	1
150230	Langer-Giedion syndrome	1
216550	Cohen syndrome	1
269700	Berardinelli lipodystrophy syndrome	1
-	Charge association	1
-	Genito-branquio- skeletal syndrome	1
-	MCA/RM and craniosynostosis	1
-	MCM/RM syndrome	2
-	Sensorineural deafness + mental retardation	2

[a] n = 11.

Table 5. CNS malformations[a]

Malformation	n
Hydrocephaly	4
Schizencephaly	2
Dandy Walker malformation	1
Corpus callosum agenesis	2
Neural tube defect	1

[a] n = 10.

Table 6. CNS dysfunction due to prenatal or postnatal origin[a]

Condition	n
Prenatal origin	n = 6
Twinning	6
Perinatal origin	n = 13
Anoxia	11
Prematurity (< 37 weeks)	2
Postnatal origin	n = 1
Kernicterus	1

[a] n = 20.

Non-classified conditions

In 87 patients (34.46%) the cause of mental retardation could not be established. The majority were mentally retarded patients with a normal phenotype and no family history of mental retardation. In table 8 the clinical findings of the patients with some abnormality in the personal or family history or physical examination are listed. Eleven patients had a mentally retarded parent or sibling. Six patients were born from a consanguineous marriage, but no specific diagnosis of an autosomal recessive disorder could be established. Eleven patients had seizures suggesting a CNS dysfunction.

Discussion

A clinical genetic approach was used in 260 patients coming from an institution for mentally retarded with the aim of establishing an etiologic cause for their impairment. With a mean age of 5.1 years this population is younger than in many institutions where the average age was 45 years (11). Therefore in some institutions where the population is younger, the majority of the individuals were from 0 to 9 years old (9). In APAE of Caxias do Sul, since the majority of facilities is guided to children, they are preferably admited. The male:female ratio of this population was 1.3:1. This is in accordance with the prevalence in the general population, which is higher in boys than in girls, ranging from 1.3:1 to 2.1:1. (15).

Table 7. Pre- or postnatal infections[a]

Infection	n
Prenatal infection	n = 3
Toxoplasmosis	1
TORCH infection	2
Postnatal infection	n = 2
Meningo-encephalitis	2

[a] n = 5.

Table 8. Clinical findings in non-classified patients[a]

Clinical findings	n
Family history of mental retardation	11
Consanguinity	6
Twinning	4
Seizures	11
Dysmorphy	8
Deafness	2

[a] n = 87.

Personal and family data were recorded and a clinical examination was performed with special interest in dysmorphology. Laboratory tests such as karyotype and metabolic screening were performed. Further auxiliary investigation such as X-rays and CT scan were performed if necessary.

With this approach a definitive diagnosis was recorded in 171 patients (65.76%). A constitutional disorder was observed in 147 patients (56.53%). A chromosomal disorder was recorded in 34.23% of the total population. Down syndrome accounted for 32.30% of the population and the other autosomal anomalies for 3.84%, including microdeletion syndromes. The frequency of chromosomal anomalies was similar to the ones observed by Gustavson et al. (32%) and Laxova et al. (32.2%), reported in 1977 (5,6). In the three Belgian studies (7,8,10) the frequency of chromosomal anomalies was lower (15.1, 13.3 and 17.6%) probably because of the institution's criteria for admission of patients (table 9). This high incidence of Down syndrome patients may be related to a precocious diagnosis which benefit an early guide to the institution. Yaqoob et al (2) reported a high incidence of Down syndrome (36%), which may be explained based on a high mean maternal age (37 years).

In 32 patients (12.30%) a Mendelian inheritance disorder was diagnosed. Thirteen were diagnosed as X-linked mental retardation. In 9 of them, Fragile X syndrome was confirmed. In the others the screening for fra (X) was negative. All presented a typical X-linked inheritance with other affected members in the family. A recent Brazilian survey of 85 institutionalized individuals with severe MR, 38 males and 47 females for Fragile X syndrome no FRAXA mutations were found (16). One of the patients with agenesis of corpus callosum presented convulsive disorder and had two maternal uncles with seizures and mental retardation. In the majority of the Mendelian disorders diagnosed there is a high incidence of mental retardation. In achondroplasia the intelligence is usually normal. The patient diagnosed with achondroplasia had hydrocephalus which contributed to the mental retardation. In ectodermal dysplasia hypohidrotic the intelligence is also usually normal. Our patient had postnatal complications as well as fever and seizures.

The incidence of acquired condition was lower than in other studies, especially due to the category of CNS dysfunction caused by pre- or postnatal conditions other than infection. In contrast, 34.46% of the population could not be fit in any diagnosis. This is higher than the previous studies listed in table 9. Fryns et al. (10) observed 30.5% of non-classified patients. Schaap et al. (12) using the same methodology studied 116 moderated to severely retarded males from another Belgian institution and could not classify 50.9% of the patients.

Probably in the non-classified category there must be mentally retarded patients due to CNS dysfunction who could not be diagnosed. Four patients were twins and 11 had seizures suggesting some CNS dysfunction. Eleven patients had a family history of mental retardation suggesting a possible genetic etiology. Sequential

Table 9. Etiological classification in mentally retarded patients

	5	6	7	8	10	Present study
	n = 122	n = 146	n = 173	n = 158	n = 262	n = 260
1.Constitutional disorders	63	67.9	42.52	45.6	42	56.53
Chromosomal anomalies	36	32.9	15.03	13.3	17.6	34.23
Down syndrome	32	32.2	12.72	9.5	16.4	32.30
Others	4	0.7	2.31	3.8	1.2	3.84
Mendelian Disorder	5	14.4	19.64	22.8	21	12.30
MCA/MR syndrome	20	3	4.05	5.7	1.9	4.23
CNS malformation	2	7.6	3.8	3.8	1.5	3.84
2. CNS dysfunction	16	14.4	34.11	20.9	19	7.69
3. Pre- or postnatal infection	7	2.8	7.51	12.7	9.9	1.92
4.Postnatally acquired conditions	1	1.4	1.73	1.9	0	0.4
5. Psychosis	2	0	1.73	1.9	0	0
6. Non-classified	12	12.3	11.56	17.7	30.5	34.46

evaluation of the patients without diagnosis could allow a delineation of a definitive diagnosis offering appropriate prognostic and reproductive counseling to the families.

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