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Profile of Patients Attended at the Genetic Service of a Special Care Institution in Brazil

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Abstract: Objective: To analyze the main etiological diagnoses of patients attended at a genetics outpatient clinic of the Association of Parents and Friends of Exceptional Children/APAE in the state of Amazonas, Brazil. Methods: retrospective study of patients seen in the period 2005-2016, with review of medical records. The following data were recorded: sex, origin of referral and etiological diagnosis. Results: 362 patients were attended, 94.7% of them from Manaus, and 5.3% from the interior of the state. The etiological diagnosis was defined in 262 (72.3%) of the sample, of which 254 (70.2%) were of genetic etiology and 8 (2.2%) non-genetic. Of the genetic etiologies, 46 (12.7%) cases were monogenic syndromes, 136 (37.6%) were chromosomal aberrations and 72 (19.9%) had multifactorial causes, however, 100 (27.6%) cases remained unclear. There were several syndromes found, with Down syndrome being the most frequent and correlating significantly with the sex of the patient (male predominance, $p < 0.05$). Conclusions: The study carried out in the APAE/Manaus genetics outpatient clinic allowed the profile of the patients being attended to be traced. It was verified that the majority of the patients were male and that the diagnosis of chromosomal alterations was the most frequent.

Key words: Medical genetics, genetic counseling, genetic profile, etiology.

1. Introduction

Medical genetics deals with particularly rare conditions, however, together they constitute a non-negligible group of diseases, with a prevalence of 31.5 to 73.0 per 1,000 individuals [1, 2]. The majority of genetically determined diseases can be classified into three main groups. The first is the chromosomal abnormalities, for example DS (down syndrome); The second is the autosomal monogenic or X-linked disorders, such as neurofibromatosis and cystic fibrosis, and the third is the group of multifactorial or complex inheritance diseases, such as congenital heart disease, mental retardation and various adult diseases, such as hypertension and cancer [3]. Approximately 5% of live births in Brazil present some genetic disease, determined totally or partially by genetic factors [4]. In addition, genetic diseases are responsible for many of the following reasons: hospitalization in a pediatric hospital, mental deficiency, neurodegenerative diseases and infertility, which aggravate the considerable effect they have on health and quality of life [5].

In Brazil, there is few care centers that offer diagnosis and genetic evaluation related to rare diseases. In a investigation regarding genetic care in Brazil [6-8], it revealed problems such as the inadequate amount of specialized consultations available, the centralization of services in large urban centers, difficulties in accessing specialized services, difficulties in referrals and counter-referrals, and the absence of the position of a medical geneticist in the Brazilian National Health System, with this professional found more frequently in research institutions and universities. This situation contributes to the lack of care for family members of the person with genetic disease. In this context, genetic pathologies appear as a public health problem and require special attention.

Non-directive genetic counseling, which is central to

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medical genetics care, is indicated for all individuals and families at risk of congenital anomaly or genetic disease. Recognizing this, the Brazilian Ministry of Health instituted, within the SUS (Brazilian National Health System), the PNAIGC (National Policy for Integral Care in Clinical Genetics).The main objective of the PNAIGC is to organize a comprehensive line of care that includes promotion, prevention, treatment and rehabilitation of patients with genetic diseases, covering all levels of healthcare and with interdisciplinary professional practice [9]. However, the lack of regulation of the PNAIGC and, consequently, of the effectuation of its proposals, renders the broad spectrum of actions proposed by this policy ineffective, which are still at the level of idealization [10].

The APAE/Manaus medical genetics outpatient clinic has a multidisciplinary group of professionals consisting of a medical geneticist, physician residents in genetics, speech therapists, physiotherapists and neurologists. It provides care to people of all ages, with any suspicion of some type of genetic anomaly sent from the various health services in Manaus, as well as from the rest of the state of Amazonas. Since it was implemented in 2007, the Genetics outpatient clinic has been working to diagnose hereditary diseases, to guide treatment for these cases and also to advise families about the risk of occurrence of these diseases in their descendants. The most common indications for referral to a genetics clinic are patients with: (1) mental retardation or developmental delay; (2) single or multiple malformations; dysmorphic syndromes; (3) inherited metabolic diseases; (4) monogenic disorders; 5) chromosomal disorders; (6) risk of genetic condition (doubts about pre-symptomatic diagnosis); (7) doubts about the genetic aspects of any medical condition; (8) couples with a history of recurrent abortions; (9) consanguinity of a couple; (10) consultation about teratogens.

Thus, the existence of few studies related to the frequency of genetic diseases, specifically in the main Brazilian centers, stimulated the elaboration of this work. The aim of the study was to perform a retrospective analysis of the genetic service performed at the APAE/Manaus, in order to highlight the importance of these services in the state. Ultimately, it is intended that this study serves as a subsidy for the construction of a comprehensive line of care for patients with genetic diseases and congenital anomalies in the region, fully included in the SUS, in accordance with the guidelines of the PNAIGC.

2. Material and Methods

A descriptive cross-sectional study was carried out based on the analysis of 316 patients (probands) attended at the Medical Genetics service of APAE/Manaus from 2005 to 2016. This service, unique in Manaus, attends patients from the SUS. The referral of patients to the outpatient clinic is performed by different services, the most frequent being: from outpatient clinics of the maternity hospitals in Manaus, from the Institute of Children's Health of Amazonas, and from the APAE itself.

The study was carried out through a structured questionnaire, the medical records were reviewed and the following parameters were evaluated: patient's age, sex, reason for the visit, city of origin, physician or institution that made the referral, complementary tests requested and, during the follow-up, final diagnosis.

The data were analyzed using the SPSS program (SPSS Inc., USA) and MINITAB v17 (MInitab Inc., USA). The first allowed, through descriptive statistics, the most prevalent diagnoses and the profile of patients seen in the outpatient clinic to be determined. Thus, data analysis was performed using qualitative variables (sex, origin, nationality, syndromic and etiological diagnoses) and quantitative variables (date of birth and age, age at the first visit, number of visits) using measure of central tendency (mean) and measure of dispersion (standard deviation). The second program allowed the estimation of the correlation between the sex of the patient such as: (a) the age at which the

disease presented in the patients, (b) the presence of DS in the patients, and (c) any type of inheritance (autosomal dominant, autosomal recessive or simple presentation of inheritance patterns) recorded in the APAE. In all cases, a p value < 0.05 was used as a criterion to consider a correlation statistically significant (α = 95%).

3. Results

From 2005 to 2016, 362 patients were treated in 615 consultations, with a mean of 1.7 consultations per year per patient. Males accounted for 219 cases (60.7%) and females for 143 cases (39.3%), with no cases of intersex. Approximately 78 patients (21.5%) were referred from other specialists in different medical centers, the most frequent being Neuropediatrics and Neurologists (28) followed by Neonatologists (16), pediatrics (12) and patients referred from the Institute of Children's Health of Amazonas (7). Of the total number of patients treated, only 138 returned for further consultations. Fig. 1 presents number of consultations per year. Table 1 shows the population evaluated according to the place of origin, sex and age of the patients at the time of the first consultation.

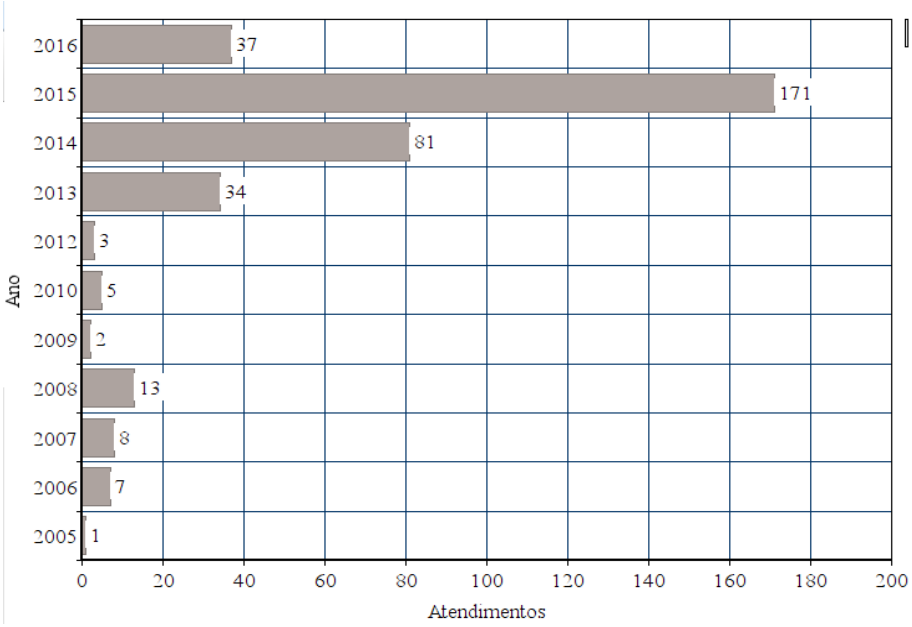

Fig. 1 Graph representing the number of consultations per year.
Ano = Year; Atendimentos = Consultations.

Table 1 Data regarding the city of origin, sex and age at the time of the consultation.

From	*N*	%
Manaus	343	94.7
Other cities	19	5.3
Age	*N*	%
< 1 year	75	20.6
1-4 years	134	37.0
5-11 years	106	29.3
12-19 years	34	9.5
> = 20 years	13	3.6
Total	362	100
Sex	*N*	%
Male	472	76.7
Female	143	23.3

The information regarding the reason for the referral, present in the referral forms of the patients or reported at the time of the consultation, allowed 4 distinct clinical situations that determined seeking specialized medical genetics care to be identified, with the appearance of the syndrome and the delay in development being most frequent (Table 2).

The etiological diagnosis was elucidated in 262 patients (72.4%), with 254 (70.1% of the total) having genetic etiology (monogenic syndromes, chromosomal aberrations and multifactorial inheritance) and 8 (2.2%) non-genetic causes. Regarding the examinations requested for the investigation, the karyotype was requested for approximately one third (n = 108) of the patients who visited the outpatient clinic and only 58 of them presented the examination at the next consultation. A total of 42 patients brought the exam results to the first consultation, while 154 did not have the karyotype exam results at the moment of data collection.

Of the genetic etiologies, 136 (37.6%) were chromosomal aberrations, 72 (19.9%) were multifactorial and 46 (12.7%) were monogenic syndromes. Reports of chromosome etiology constituted the majority of diagnoses with genetic etiology, with Down syndrome being the most frequent ($p < 0.005$) (Fig. 2).

The multifactorial etiology was responsible for 19.9% of the cases, with overall developmental delays being the most frequent, followed by inborn errors of metabolism. In this group, 72 patients were referred due to learning difficulties, delayed in some area of development or changes in behavior.

Only 8 patients (2.2%) had other non-genetic causes for the malformation. The most common reason for malformations in this group was the use by the pregnant woman of the drug misoprostol (3 cases), and cerebral palsy (2 cases). The main malformation due to misoprostol was Moebius syndrome.

The autosomal dominant diseases prevailed in relation

Table 2 Reason for the referral to the genetics outpatient clinic.

Reasons for (*f*)	N	%
Syndromic Appearance	176	48.6
RDNPM	89	24.6
Altered neonatal screening	28	7.7
Growth deficit	5	1.4
Others	64	17.7
Total	362	100

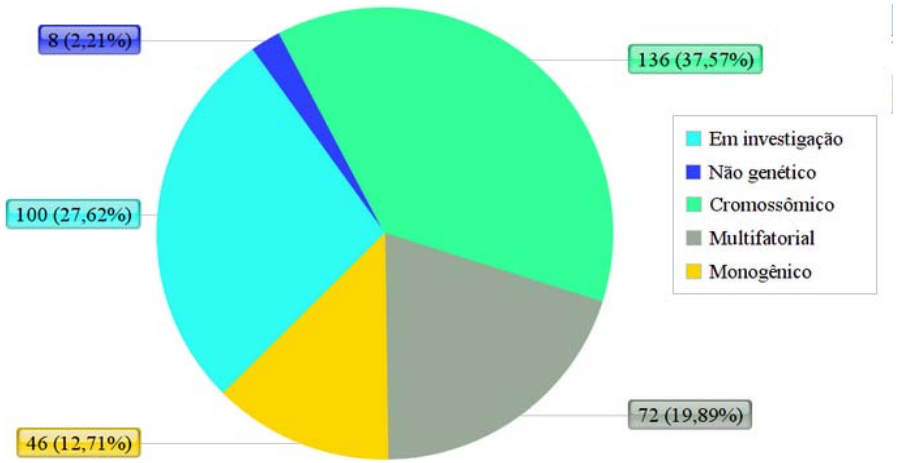

Fig. 2 Main etiologies identified.
Em investgação = Under investigation; Não genetic = Non-genetic; Cromossômico = Chromosomal; Multifatorial = Multifactorial; Monogênico = Monogenic.

Table 3 Diseases diagnosed in the genetics consultations of APAE.

Autosomal dominant	*N* patients
Skeletal dysplasia	5
Achondroplasia	5
Noonan syndrome	3
Cornelia de Lange syndrome	2
Sotos syndrome	2
Crouzon syndrome	2
Cardiofacialcutaneous syndrome	1
Costello syndrome	1
Marshall-Smith syndrome	1
Congenita cutis laxa syndrome + consanguinity	1
Holt-Oram syndrome	1
Ehlers-Danlos syndrome	1
Craniosynostosis	1
Pseudoachondroplasia	1
Apert syndrome	1
Axenfeld-Rieger Syndrome	1
Neurofibromatosis	1
Loeys-Dietz syndrome	1
Treacher Collins Syndrome	1
Tuberous Sclerosis	1
Rubinstein-Taybi syndrome	1
TOTAL	29
Autosomal recessive	*N* patients
Gaucher's disease	1
Bloom syndrome	2
Gangliosidosis (GM1)	1
Spinal muscular atrophy type 1	1
Microcephaly	1
Berardinelli syndrome	1
Peters plus syndrome	1
Seckel syndrome	1
Microcephaly + consanguinity	1
TOTAL	10
Presenting two to three patterns of inheritance	*N* patients
Intellectual Deficiency	66
Global development delay	41
Autism	4
Muscular dystrophy	2
Inborn error of metabolism	1
Charcot-Marie-Tooth disease	1
Coffin-Siris syndrome	1
Osteogenesis imperfecta	1
Aicardi syndrome	1
Epilepsy	1
Hypomelanosis of Ito syndrome	1
Ichthyosis	1
TOTAL	121

to the recessive diseases. Among the dominant and monogenic diseases, the most frequent were Achondroplasia and Skeletal dysplasia. With regard to the diseases of autosomal recessive etiology, it was observed that some of those affected were not children of consanguineous couples, except in nine cases. In relation to consanguinity, it must first be remembered that, being distant and not between first cousins, the risk for genetic pathologies becomes smaller (Table 3).

The sex of the patient had a statistically significant relationship with the presence or not of DS in the patients analyzed (X^2 = 4.437, DF = 1, p = 0.035), being more present in men than in women. The estimated sex ratio (males: females) was 1.6. There was no evidence of a relationship between the sex and the age at which the disease occurred in the patients (X^2 = 3.930, DF = 6, p = 0.666), nor with the type of inheritance (autosomal dominant, autosomal recessive or other) of the diseases registered in the patients (X^2 = 0.440, DF = 2, p = 0.802).

4. Discussion

Statistics indicate that nine out of ten causes of death and/or disability prevalent in the world population are genetically predisposed. These statistics position genomics in the field of public health, since these disorders not only tend to have an unfavorable impact on the affected individual, but also generate a large and unexpected social burden for the families affected and society. Thus, genetic diseases appear as a public health problem making it necessary to better discuss and investigate them [2, 11-14].

Despite the above, the city of Manaus lacks this kind of care. The genetics outpatient clinic that currently operates in one of the APAE units in the state of Amazonas is the only center dedicated to genetic diseases, and treats patients with malformations from the capital and the interior of the state. The service has been operating for 11 years and has attended 362 children. The number of consultations is far below the demand and, for reasons such as the lack of outpatient care spaces, many patients do not have access to the service, demonstrating the need to expand it. Several authors report the lack of specialized centers and especially the lack of professionals qualified for the demand as the main cause of the low number of consultations. In addition to this, the majority of Latin American countries do not present an explicit health policy or financial support for the prevention and treatment of genetic disorders [6-8, 11].

Some of the patients are referred from other specialties and from various health care centers. The consultation with the family members of the malformation patient is the most complete source of investigation in the majority of cases since the patients do not have a complementary medical history, with the same situation observed by Bertola [15].

In the sample, there was a predominance of males, corroborating what was observed by Bertola [15] and Fontinelle [14]. However, other studies published present variations between the predominance of males or females, depending on the location and service analyzed [16, 17].

Approximately 30% of the cases did not have their etiology determined. Most of the cases without diagnosis were patients with mental retardation or developmental delays. The lack of conclusive diagnosis for the congenital malformation has also been reported in the literature and highlights the need for the development of new diagnostic techniques, especially molecular biology techniques [18, 19].

Regarding the examinations requested for the investigation, the karyotype was requested for approximately one third of the patients who visited the outpatient clinic. Repeated abortions, mental retardation and congenital anomalies are associated with chromosomal disorders and affect about one in 150 live-born infants [20, 21].

In this study, a high frequency of chromosomal aberrations (37.6% of the cases) was observed among the patients attended at the outpatient clinic. In other studies carried out in different genetic centers in the

country, prevalence rates of between 15% and 29% of chromosomal aberrations among the investigated patients were also observed [2, 11, 15, 22-25]. It should be highlighted that most of the patients attended came from the APAE/Manaus causing a possible bias in the sample.

The diseases with multifactorial etiology accounted for approximately 20% of the patients treated, this type of disorder results from the combination of various genetic and environmental causes. Studies have reported that the impact of multifactorial diseases varies from 5% in the pediatric population to more than 60% in the general population [4, 26].

Regarding the type of genetic inheritance, autosomal dominant diseases of the monogenic type were more frequent, with the most common pathologies being Achondroplasia and Skeletal dysplasia. Although individually rare, monogenic diseases account for high rates of morbidity and mortality, with approximately 2% of the population being affected at some point in life. Examples of these disorders include cystic fibrosis and sickle cell anemia, among others [27]. In a study of US patients, it was estimated that the incidence of monogenic disorders in the pediatric population was 0.36%. However, when analyzing the causes of hospitalization in children of this population, this number rose to between 6 and 8% [26, 28].

There were patients treated in the outpatient clinic that presented some kind of apparently genetic anomaly, which, when investigated, were found to be non-genetic diseases caused by environmental factors, such as cerebral palsy (2 cases) and diseases caused by the use of teratogenic agents, such as misoprostol, leading to Moebius syndrome (3 cases). In the literature on the subject, there are many studies that report the correlation of congenital anomalies with the maternal use misoprostol and the ingestion of alcohol during pregnancy. The external factors were proposed as the cause of these anomalies due to the increase in the number of cases of the syndrome associated with the use of misoprostol during pregnancy [29-32].

Regarding the existence of a significant correlation between the sex of the patient and the presence of DS, it is likely that this is associated with the sampling performed, considering that the evaluation was performed in a single service center, excluding unregistered cases. Despite this, some recent studies show results similar to those found in this study regarding a statistically significant trend of male patients with DS. In a 2002 study, Kovaleva et al. [33], in a review of 55 scientific publications on DS in various parts of the world, showed this as a systematic and consistent trend. The authors also reported the ratio between the sexes for DS (male: female) and concluded that there was an increase from 1.35 (1940's) to 1.3-1.62 (1980's), coinciding with that obtained in the present study, which was 1.6. The authors related two genetic mechanisms to this trend of predominance of DS among men. The first was the joint segregation of chromosome 21 and the Y chromosome in spermatogenesis. The second was chromatid nondisjunction during the second meiotic division of oogenesis caused by the sperm carrying the Y chromosome.

5. Conclusions

The set of results allowed us to know the profile of patients seen at the genetics outpatient clinic of the Association of Parents and Friends of the Exceptional/APAE-AM. It was possible to verify that the number of boys affected with genetic anomalies is greater than the number of girls. This statistic in Apae is associated with the consequence of the many genes of mental deficiency linked to the X chromosome, given epidemiologically known even before these genes were mapped. Information gathered provides insights to enhance clinical protocols in order to optimize and streamline case management and evidence-based piping and patient-specific health needs. Two important limitations of the study are the reduced number of consultations per patient that often interrupts treatment during the diagnostic investigation

period, and of cases as yet undiagnosed, which, in this group, strongly depends on the study of genes not yet available in the SUS. In spite of this, one aspect of great relevance would be the establishment of partnerships with research institutions for access to diagnostic tests. Locally, the challenge is the effective incorporation of other specialties in this proposal, from the perspective of the multidisciplinary approach in line with the guidelines and principles of the National Policy for Comprehensive Care for People with Rare Diseases.

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