Clinical description of 41 Brazilian patients with oculo-auriculo--vertebral dysplasia

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Summary

Objective: To describe the most prominent clinical features of a cohort of patients with oculo-auriculo-vertebral (OAV) dysplasia in Brazil.
Method: A review of medical records of patients with diagnosis of OAV from 1990 to 2010 was performed in a medical genetics center.
Results: 41 patients were included in the study. Their average age at diagnosis was 2y 10mo (34,4±48,8 months) and the female proportion was 53.7%. Mean maternal age at patient's birth was 28.5y (min: 17, max: 46y) for mothers and 31.4y (min: 21, max: 51y) for fathers. Most patients (97.5%) had auricular involvement, with facial manifestation in 90.2%, spinal in 65.9%, ocular in 53.7%, 36.6% with cardiovascular involvement, 29.3% urogenital, and 17% of the cases with central nervous system (CNS) involvement. The classic OAV triad was present in only 34%. All patients except one had concomitant problems in other organs or systems.
Conclusion: Since the diagnosis of OAV dysplasia relies only on a comprehensive medical evaluation, it is imperative that clinicians be aware of the most common presentation of the syndrome. Once suspected, every patient should undergo a complete medical evaluation of multiple systems including complementary exams. Treatment of these patients is based on surgical correction of malformations and rehabilitation.

Keywords: Goldenhar syndrome, facial asymmetry, craniofacial abnormalities.

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Introduction

The Goldenhar syndrome was described in 1845 by Carl Ferdinand von Arlt and recognized as a clinical entity in 1952 by Maurice Goldenhar who described it in a child, as reported Salvitti et al.[1] It has been known as first branchial arch syndrome, Gorlin's syndrome and hemifacial microsomia (OMIM 164210), but currently it is best known as oculo-auriculo-vertebral (OAV) dysplasia, a nomenclature given by Gorlin et al.[2] and Sugar.[3]

Its prevalence has been estimated at about one case per 5,600 to 26,550 births,[4-6] with greater involvement of males than females (in a ratio of about 3:2).[7] The cases are mostly sporadic, but families with autosomal recessive or autosomal dominant inheritance have been described;[8,9] thus, the hypothesis that there is no kind of genetic factor involved that would influence susceptibility to the disease has been ruled out.[10] In this regard, reports of monozygotic twins,[11] both dichorionic and monochorionic,[12] discordant for the disease have been made, suggesting a correlation with a multifactorial inheritance pattern.

Moreover, there is evidence in the literature indicating that ingestion of certain drugs, such as thalidomide, retinoic acid, tamoxifen and cocaine during pregnancy can be related to the development of this condition. Other factors have been suggested as etiological factors include maternal diabetes, viral infections (e.g. rubella and influenza) and

the abuse of alcohol during pregnancy as well.[13-15] Mounoud et al. reported a case of OAV dysplasia in a child whose mother had a history of hypervitaminosis A. It is known that daily doses of vitamin A higher than 25,000 IU have teratogenic effects. This teratogen has harmful effects in the formation of neural crest cells, which are essential for the formation of the pharyngeal arches.[16,17]

Affected individuals may present: malar and/or mandibular hypoplasia, hypoplasia of the facial muscles, microtia, preauricular tags and outer ear dysplasia, hemivertebrae and hypoplasia of cervical thoracic or lumbar vertebrae, epibulbar dermoids, microphthalmia, cleft palate and/or lip, cardiac, kidney or central nervous system (CNS) anomalies.[2] In addition, there are reports on the association of OAV dysplasia with other conditions, such as genitourinary,[18,19] cardiovascular,[14,20] or psychiatric[21,22] changes, and obstructive sleep apnea.[23] However, due to clinical variability, some patients have minimal manifestations, predominantly facial asymmetry and dysplasia of the auricular pavilion.[2]

Based on the above, and considering the importance of the topic due to prevalence, wide spectrum of clinical manifestations and the lack of studies that describe a significant number of patients suffering from OAV dysplasia in our midst, we describe a case series of patients diagnosed with OAV dysplasia followed in our service over the past 20 years.

Method

The sample consisted of individuals followed in the Medical Genetics Unit at Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (ICr-HC-FMUSP), diagnosed with OAV dysplasia from 1990 to 2010. This study was approved by the Ethics Committee for Research Project Analysis – CAPPesq of HC-FMUSP (No. 0667-07).

Patients included in the study were those with normal G-banding karyotype and involvement of at least two of the following sites: 1) mouth, skull and face, 2) eyes, 3) ears and 4) vertebrae. This approach was consistent with that adopted by Strömland et al. (2007).[12] Individuals with chromosomal abnormalities or incomplete medical records were excluded from the study.

We conducted a retrospective analysis, and collected data on clinical manifestations (ear, face, spine, eyes and more), demographics (gender, date of birth, age at first consultation, and age of parents) and results of additional tests. The affected side (right, left or bilateral) was that where microtia or facial microsomia was located, similarly to the method adopted by Rollnick et al. (1987).[24]

Results

Among the 41 patients studied, 19 (46.3%) were male and 22 (53.7%) female. The mean age at first consultation was 2 years and 10 months (34.4±48.8 months). The mean age of parents at the birth of the child in cases where information was available (39/41 patients) was 28.5±6.9 years for the mothers and 31.4±7.4 years for the fathers.

With regard to clinical manifestations, 97.5% of the patients had some degree of ear involvement, 90.2% facial, 65.9% vertebral, and 53.7% ocular. 89% of children had involvement of other organs. The classic OAV triad was present in only 34% (15 children). All patients except one had concomitant problems in other organs or systems.

Facial manifestations

Facial abnormalities were observed in 90.2% (37/41) of patients. Of these, 83.8% (31/37) had some degree of hemifacial microsomia. In 46% (17/37) of the cases, change in facial expression was observed, suggesting some degree of facial paralysis. We also found that 14% (6/37) of the cases had cleft palate and/or lip and 7% (3/37) had ocular hypertelorism.

Ocular manifestations

From the classic triad of changes described as OAV dysplasia, ocular changes were less frequent in our series, with about 53.7% (22/41) of patients presenting some involvement. Epibulbar dermoids or dermoid cysts were seen in 45.4% (10/22), representing the vast majority in the group of eye diseases, followed by the finding of epicanthus, present in 22.7% (5/22) and other epibulbar tumors, present in 13.6% (3/22). Other ocular manifestations found in our series at a lower prevalence (1 or 2 cases) are: coloboma, changes in the lacrimal gland, anophthalmia and amaurosis.

Auricular manifestations

In terms of location, 30% (12/40) of patients had involvement limited to the right side, 30% (12/40) had abnormalities only in the left side, and 40% (16/40) were affected bilaterally. The most commonly found malformation was that of auricular dysplasia to varying degrees in 73% (30/41). The presence of preauricular tags occurred in 51.2% (21/41) of cases. In 24.4% (10/41) of patients, these two manifestations were simultaneous. In 31.7% (13/41) of cases, some degree of functional hearing loss was reported. Other changes described, by order of prevalence, are: auditory canal stenosis in 14.6% (6/41), auditory canal agenesis in 12.2% (5/41), abnormal implantation of the pinna in 9.8% (4/41), and recurrent acute otitis media in 7.3% (3/41).

Vertebral manifestations

65.9% (27/41) of the patients had vertebral abnormalities. Of these, spinal axis changes were found most often including marked kyphosis and/or scoliosis in 48.2% (13/27) of cases. Localized vertebral involvements were also prevalent, including the finding of hemivertebrae in 37% (10/27) cases, most often in the thoracic segment with 25% (7/27) patients affected. Block or fused vertebrae were diagnosed in 33% (9/27) of cases, with greater involvement of the cervical spine, affected in 77.7% (7/9) of patients, as well as the presence of incomplete fusion of vertebral arches in 14.8% (4/27) of the patients. Other reports included: sacral dimples in 22% (6/27) of patients, spina bifida in 14.8% (4/27), and transitional vertebrae in 14.8% (4/27).

Other systemic manifestations

Cardiovascular system

Cardiovascular involvement was found in 36.6% (15/41) of the patients. The spectrum is quite heterogeneous, but the most frequent changes were communications between heart chambers, which were present in 36.6% of the patients with cardiac involvement. Interatrial communication was responsible for 40% (6/15) of the cases, and ventricular septal defects for 33.3% (5/15) of the cases. Complex congenital heart disease were seen in 26.7% (4/15) patients, the most common being the tetralogy of Fallot, present in 50% (2/4) of cases. Persistent arterial duct was found in 20% (3/15) of the patients.

Urogenital system

In our sample, 29.3% (12/41) of patients showed abnormalities in the urinary tract, of which 41.7% (5/12) had concomitant change in the cardiovascular system. Among the abnormalities found, pelvic kidneys and unilateral renal agenesis were the most prevalent occurrences, both present in 41.7% (5/12) patients each. Of note, among patients diagnosed with pelvic kidney, 80% (4/5) had ipsilateral ear involvement. Other changes less frequently observed (1 or 2 cases) were pyelocaliceal ectasia, pyeloureteral duplication, vesicoureteral reflux and hypospadias.

Central nervous system

17% (7/41) of the patients had CNS changes, especially expansion of the cerebral ventricles, found in 43% (03/07) of cases. 28.6% (2/7) of these cases had dysgenesis of the *corpus callosum* associated with ventriculomegaly, and 14.3% (1/7) showed absence of the septum pellucidum associated with ventriculomegaly. Occipital encephalocele associated with posterior parietal meningoencephalocele was less frequent alteration found in one patient.

Discussion

OAV dysplasia is a well-defined entity, characterized by unilateral or bilateral craniofacial anomalies, to a variable degree, involving the first and second branchial arches, and vertebral and eye abnormalities. Clinically, it varies from an isolated microtia, with or without mandibular hypoplasia, to a more complex phenotype involving skeletal, cardiac, renal, lung and CNS disorders.[24,25]

As previously mentioned, much has been speculated about the etiological and pathogenic mechanisms that lead to the development of OAV dysplasia. In this sense, several studies have been performed to identify genetic changes that may be related to the phenotype displayed by patients with OAV, but so far such correlation could not be established.[26]

Our results reveal that 21 (48%) patients were male and 23 (52%) were female, a proportion similar to that found in a study conducted in the city of Bauru, state of São Paulo,[27] and different from that observed in other studies that found male predominance with a ratio of 3:2.[7]

Regarding the therapeutic approach, in less complex cases interventions vary according to the age and systemic involvement and are mainly intended to improve esthetics. In patients with mandibular hypoplasia, reconstructive surgery can be performed using bone grafts taken from the ribs and, in some instances, bone stretching. In cases where there is cleft lip and/or palate, surgical correction is usually performed followed by the use of orthodontic devices after correction of mandibular defects.

Reconstructive surgery to correct auricular malformation is usually performed at the age of 6 to 8 years. In patients with milder involvement, mandibular reconstruction surgery can be performed in early adolescence. Epibulbar dermoids must be removed surgically. Structural ocular anomalies and those of the outer ear should be corrected by plastic surgeons.

Conclusion

It is important to emphasize that individuals with OAV dysplasia often have psychosocial difficulties caused by stigma. Thus, the participation of a multidisciplinary team is crucial so that patients can be addressed globally for proper support. In general, the prognosis is good, especially in cases without systemic involvement. More severe cases of OAV dysplasia can affect many aspects of a patient's life, and many require interventions shortly after birth.[2,14]

TABLE 1 Type and frequency of changes observed in patients with OAV dysplasia.

Type of change	n	%
Auricular	40/41	97.5
Dysplastic pinna	30/40	75
Preauricular tags	21/40	52.5
Hearing loss	13/40	32.5
Auditory canal stenosis	6/40	15
Abnormal implantation of the ears	4/40	10
Recurrent otitis media	3/40	7.5
Facial	37/41	90.2
Hemifacial microsomia	31/37	83.8
Change in facial expression	17/37	46
Cleft lip and/or palate	6/37	16.2
Ocular hypertelorism	3/37	8.1
Vertebral	27/41	65.9
Kyphosis/scoliosis	13/27	48.2
Hemivertebrae	10/27	37
Block/fused vertebrae	9/27	33.3
Sacral dimple	6/27	22.2
Spina bifida	4/27	14.8
Incomplete fusion of vertebral arches	4/27	14.8
Transitional vertebrae	4/27	14.8
Ocular	22/41	53.7
Epibulbar dermoids	10/22	45.4
Epicanthus	5/22	22.7
Other epibulbar tumors	3/22	13.6
Coloboma	1/22	4.6
Anophthalmia	1/22	4.6
Amaurosis	1/22	4.6
Cardiovascular	15/41	36.6
Interatrial communication	6/15	40
Interventricular communication	5/15	33.3
Complex cardiopathy	4/15	26.7
Persistent arterial duct	3/15	20
Urogenital	12/41	29.3
Pelvic kidney	5/12	41.7
Renal agenesis	5/12	41.7
Pyelocaliceal ectasia	1/12	8.3
Pyeloureteral duplication	1/12	8.3
Vesicoureteral reflux	1/12	8.3
Hypospadias	2/12	16.6
Central nervous system	7/41	17
Expansion of the cerebral ventricles	3/7	43
Dysgenesis of the corpus callosum	2/7	28.6
Absence of the septum pellucidum	1/7	14.3
Occipital encephalocele with posterior parietal meningoencephalocele	1/7	14.3

Resumo

Displasia óculo-aurículo-vertebral: aspectos clínicos de 41 pacientes brasileiros

Objetivo: descrever os principais achados clínicos de uma coorte de pacientes com a displasia óculo-aurículo-vertebral (OAV).
Método: revisão de prontuários médicos dos pacientes com diagnóstico de OAV no período de 1990 a 2010, acompanhados em um centro de genética médica.
Resultados: foram incluídos no estudo 41 pacientes. A média de idade ao diagnóstico foi de 2 anos e 10 meses (34,4±48,8 meses) e a proporção de pacientes do sexo feminino foi de 53,7%. A média de idade dos pais ao nascimento do paciente foi de 28,5±6,9 anos para as mães e 31,4±7,4 anos para os pais. A maioria dos indivíduos (97,5%) possuía acometimento auricular, 90,2% tinham manifestações faciais, 65,9%, vertebrais, 53,7%, oculares, 36,6%, cardiovasculares, 29,3%, urogenitais e 17%, no sistema nervoso central. Além disso, 34% dos pacientes apresentavam a tríade clássica óculo-aurículo-vertebral, e todos os pacientes exceto um apresentavam concomitantemente problemas em outros órgãos ou sistemas.
Conclusão: já que o diagnóstico desta entidade é eminentemente clínico, é imprescindível que os médicos das mais diversas especialidades conheçam os achados mais frequentes na OAV. Diante de um paciente com suspeita diagnóstica, deve ser realizada avaliação detalhada de outros órgãos, tanto clínica como por meio de exames complementares. O tratamento é baseado na correção cirúrgica das malformações e na reabilitação.

Palavras-chave: síndrome de Goldenhar, assimetria facial, anormalidades craniofaciais.

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