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ORIGINAL ARTICLE

Audiological and clinical management of children with oculo-auriculo-vertebral spectrum

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Abstract

Oculo-auriculo-vertebral spectrum is a rare, heterogeneous congenital condition, of unknown aetiology, mainly involving the ear (microtia) and jaw (hemifacial microsomia). In addition to those structures originating from the first and second pharyngeal arches, multiple systems can be affected.

ENT specialists and audiologists may focus their attention on the microtia and its effect on the hearing capacity of the child, but it may be only a sign of a more complex spectrum of abnormalities. A complete study of auditory function is crucial, but not exclusively. Proper management would consider the neuroradiological study not only of the whole hearing organ, but also of the cranial nerves, soft tissues and craniofacial structures. A geneticist should investigate the family history in order to identify a specific pattern of inheritance. A maxillofacial surgeon and orthodontic assessment may be appropriate when patients present with hemifacial microsomia; an ophthalmological evaluation should be considered when ocular impairment is evident or suspected.

A total body examination is crucial to disclose abnormalities involving other organs or systems. If further malformations are suspected, then additional radiological investigation and a specialist examination may be warranted.

Key words: *oculo-auriculo-vertebral spectrum, Goldenhar syndrome, microtia, hemifacial microsomia*

Introduction

Oculo-auriculo-vertebral spectrum (OAVS) (OMIM 164210) (1) is a rare, heterogeneous congenital condition (male:female ratio 3:2, incidence 1:3500–5600 live births) (2–4), in which patients' facial features originating from the first and second pharyngeal arches are incompletely developed on one (85% of cases) or both sides (3,5).

The disease mainly involves abnormalities of the ear (microtia) and jaw (hemifacial microsomia). The eye or spine is also affected in the most severe cases, when the condition is known as Goldenhar syndrome after the French ophthalmologist who first described this combination of malformations in 1952 (6). A family history suggestive of both an autosomal recessive and a dominant inheritance has been reported, and genes on several chromosomes (e.g. chromosomes 5, 12, 14 and 22) (7–10) have been implicated, but most cases of OAVS are sporadic with no known aetiology. An abnormal embryonic vascular supply (11), haematomas and drugs used in the early phases of gestation have been cited as disrupting mesodermal migration, leading to a defective formation of bone and soft tissue structures (12).

While the facial involvement (ear, mandible, soft tissues, facial muscles, skull, eye, cranial nerves, etc.) is characteristic of OAVS, multiple systems (skeletal, cardiovascular, CNS, urogenital, etc.) may also be affected, with abnormalities that vary in both type and severity.

This paper aims to describe the phenotypic variability of OAVS patients focusing on those features that might challenge their management.

Discussion

Microtia, atresia and concomitant inner ear abnormalities

Microtia is a congenital malformation of the external ear. This auricular defect can sometimes be one of a

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number of abnormalities also affecting other areas, as in OAVS, but in most cases microtia is an isolated condition (prevalence 0.83–17.4/10,000 lives) (5,13,14). Most cases are unilateral (in 79–93% of cases), with a predilection for the right side (60%), but both sides may be more or less severely affected (5,13–15).

Only 2% of patients have a positive family history (16,17). Since the structures involved originate from the I and II branchial arches, the association of microtia and stenosis/atresia of the external acoustic meatus is frequent, and pre-auricular tags, fistulas and middle ear conditions (involving the tympanic cavity, ossicular chain, etc.) are not uncommon findings (13,18,19). Consequently, conductive hearing loss is the most frequent auditory deficit in patients presenting with microtia. Nevertheless, sensorineural or mixed hearing loss is also reported. A recent study that also reviewed all available literature data, showed that in about 30% of OAVS patients the inner ear might be abnormal (vestibulo-cochlear dysplasia ranging from common cavity deformity to anomalies of the semicircular canals have been reported – thus highlighting that the noxa acting on the first and second pharyngeal arches might have a more widespread effect on intrauterine development) (20,21).

It is worth noting that most recent studies suggest that microtia should be considered the least severe feature of OAVS (96).

Patients' perception capacity is naturally reduced in cases of unilateral hearing loss, and even more so in bilaterally affected patients, with a consequent impairment of their ability to communicate (13).

It is well known that the sooner a hearing loss is identified the better the patient's outcome. An appropriate hearing aid (a prosthesis or cochlear implant) and a regular follow-up are usually needed to monitor hearing and language acquisition during childhood.

In addition, patients with isolated microtia only have auditory impairments, but OAVS patients may also have cranial nerve, facial muscle and skeletal abnormalities, with cumulative negative effects on the development of normal communication skills (in both perception and production), oral function (praxis and sensitivity), and ability to swallow.

For all these reasons, ENT specialists and audiological physicians can have a pivotal role in the early years of patient management and they should be prepared to deal with children who need a global healthcare approach.

Do not underestimate a microtia/atresia

When assessing a patient presenting with microtia/atresia, it is important to remember that the ear may be only one of the areas involved. Patients must always undergo a thorough physical examination, including an in-depth evaluation of the ear, nose, throat, head and neck, along with an overall assessment of their general physical and neurological status (22).

Microtia/atresia may be isolated, but it is always wise to check for other features potentially linking microtia with a more complex spectrum or syndrome. Before looking on the abnormal side, the normal ear should be assessed. In some cases, even when the lobe seems normal, with no pre-auricular tags or fistulas, the external auditory canal (EAC) may be atresic or stenotic. The shape, size, position, course and calibre of the EAC, as well as the otoscopic appearance of the tympanic membrane, can serve as a useful benchmark for analysing the affected side. If both sides are abnormal, the examination should begin from the least involved side. This brief physical examination can shed light on severe malformations, especially by helping to understand the altered structures when the anatomy is very complicated.

The abnormal ear should then be considered; its shape and position may be different from the normal ear on the other side. Although, to date, no diagnostic criteria have been established for microtia, several classifications have been proposed by various authors (e.g. Marx (23), Tasse (16)) as well as OMENS classification (24). Marx classifies an abnormal auricle as: grade I when its shape is normal but its size is reduced; grade II when it is abnormal and hypoplastic, but all anatomical structures are still recognizable; or grade III when it shows severe deformity with only skin upheaval (16,25,26). Pre-auricular tags or fistulas are often seen on the affected side (special attention should be paid to their position and mutual relationship with the residual auricular lobe).

On examination of the oral structures, abnormalities may involve the palate (e.g. cleft lip and palate), choanae and oral pharynx. These regions can also show functional impairment (due to the abnormal anatomy or to cranial nerve functional impairments). After examining the oral structures, the whole head should be assessed, checking the symmetry of the face. When asymmetry is evident, a closer examination of soft tissues, jaws or zygomatic arches may reveal which of these components is responsible for any hemifacial microsomia. The position of the chin can also help to determine if one of the hemi-mandibles is shorter than the other.

Although this clinical examination can be indicative, only neuroradiological investigations (CT and MRI) can provide effective diagnostic information about the asymmetry of the above-mentioned facial structures.

When assessing the ocular apparatus, the position and size of the orbits, eyeball abnormalities (such as

epibulbar dermoids, microphthalmia, coloboma, etc.) are possible features to look for. Altered ocular movements can also provide crucial information, revealing defects of the III, IV or VI cranial nerves.

In subjects presenting with multiple abnormalities of the facial structures, as in Goldenhar syndrome, dysmorphic vertebral bodies and the fusion of multiple cervical vertebrae may give rise to particular head positions, suggesting the need for a further analysis of the neck structures (such as neuroradiological examination).

Cranial nerve clinical evaluation of ocular movements, facial motility and sensitivity is always appropriate. Facial motility impairment may, however, be evident when the patient cries or smiles, either during spontaneous interactions with the physician or with the parents, who may even report this information. A neurologist should attend if the ENT specialist or audiological physician is unfamiliar with II, III, IV, V, VI and VII cranial nerve assessment.

It is also always useful to ask if previous examinations had suggested abnormalities in other body regions.

A quick check-up can reveal whether the malformation is isolated, part of a syndrome (e.g. Treacher-Collins, branchio-oto-renal, CHARGE syndrome, etc.), or part of a spectrum of abnormalities such as OAVS. This information is crucial in deciding the next diagnostic and therapeutic steps.

Hearing first

Whether the patient has an isolated auricular malformation or a wider spectrum of abnormalities, a complete assessment of hearing function is essential (27). Early diagnosis and appropriate intervention are known to be crucial to providing the best opportunity for appropriate counselling, habilitation and development (22).

Deafness does not only affect a patient's quality of life, it also carries a burden of costs for health care, special education and other services, as well as limiting the patient's potential for learning and earning. Unilateral hearing loss coincides with a limited capacity to discern and locate sounds against background noise. In some cases, as in OAVS, deafness may be associated with visual impairments too, and when both senses are involved the impact on communication and education may be huge (22).

Auditory brainstem responses, speech and tonal audiometry, tympanometry and acoustic reflex threshold measurements, and otoacoustic emissions are useful methods for assessing the presence, degree and nature of hearing impairments. Children showing syndromic features should be screened early and routinely for hearing loss, and parents should be made aware of the risk and questioned about their child's hearing and language milestones (22).

Auditory brainstem response tests (air and bone conduction thresholds) and otoacoustic emissions should be used in the initial assessment of auditory capacity and for the early selection of patients eligible for hearing aids.

A strict follow-up regime is important in the management of unilateral hearing loss. The first priority is to establish whether the hearing loss is conductive, neurosensory or mixed, and to grade the deficit. In recent articles, some authors have suggested treating the affected ear with bone conduction hearing aids (28). In addition to adopting and managing any such prosthetics, careful monitoring of the normal-hearing side is also pivotal: when hearing is impaired in one ear, the other must 'take responsibility' for preserving the patient's detection capacity. When both ears are involved, an in-depth assessment of hearing function is crucial because the best treatment could be a hearing aid in some cases (bone or air conduction hearing aids), cochlear implants in others.

External ear malformations may be only a part of the hearing organ's problems, such as in LAMM syndrome in which microtia is associated with labyrinthine aplasia (29), so CT or CONE BEAM CT and MRI should be used to check the middle and inner ear and provide additional information (see below). Neuroradiological assessment is also useful whenever patients are being considered for plastic surgery to reconstruct the external ear.

Altered oral function and language production difficulties may warrant speech and language therapy, while impairment due to anatomical abnormalities could require surgery.

Neuroradiological examination

CT is a powerful tool for investigating 'in vivo' the bone and soft tissue structures of the ear and is considered pivotal in the diagnostic work-up of microtia and in its surgical planning. In addition, in the last few years neuroimaging (especially MRI) has become important in OAVS patients for the evaluation of other structures of the head such as the central nervous system, cranial nerves, intracranial vessels, facial muscles and skull bones, that might be variously involved in this condition.

High-resolution CT with less than 1-mm-thick slices provides a precise visualization of the bones of the external acoustic meatus, ossicular chain, and inner ear. This examination may be used to score the severity of atresia, the presence of a bone or cartilaginous wall, the severity of ossicular chain dysplasia, the presence of air in the tympanic air cells and the coexistence of inner ear abnormalities that might

require a different tailored surgical approach. As is generally recognized, functional surgery for congenital aural atresia is difficult, thus the risk of the operation may outweigh the potential benefits (30). A preoperative temporal bone CT scan and the appearance of the external ear can be used as parameters in order to develop grading schemes; the grade assigned preoperatively, in previous studies, has been shown to correlate well with the patient's chance of success (30). Moreover, CT might provide valuable information about facial asymmetry allowing the evaluation of bone and soft tissue involvement and representation of the defects by means of 3D reconstructions. These data might be helpful in planning and improving reconstructive or aesthetic maxillofacial surgery.

New imaging approaches, such as CONE BEAM CT, seem to provide equivalent, if not better quality, images of the bone structures allowing a significant reduction of X-ray exposure, an important issue especially when dealing with paediatric patients.

Magnetic resonance imaging completes the neuroradiological investigations. High soft-tissue contrast makes MRI ideal for evaluation of the inner ear, internal auditory canal and cerebellopontine angle.

MRI can also give crucial information about facial muscles and soft-tissues hypoplasia or absence, and should be considered the gold standard for evaluating cranial nerves abnormalities. Information about the presence, course and calibre of VII and VIII cranial nerves might be pivotal in the decision-making process when evaluating whether those patients are eligible for cochlear implantation. In addition, the presence of concomitant brain abnormalities (pons cleft (31), tegmental cap or severe brain involvement), might also influence other approaches such as brainstem implantation. Additional information about the vascular supply of the inner ear and the CNS system, can be useful for those patients undergoing canaloplasty, ossicular reconstruction, or major surgery such as cochlear implantation, plastic surgery or neurosurgery. Major surgery may need more detailed information about the vascular supply of specific regions, so MR angiography can be a valuable resource.

Global healthcare approach

Although any physician may diagnose OAVS or Goldenhar syndrome, it is always appropriate to consult a specialist in genetics who can confirm the diagnosis. The diagnostic process can be very challenging, for example when clinical features may be overlapping between two different craniofacial syndromes (as reported between OAVS and branchio-oto-renal syndrome) (32).

A geneticist should investigate the family history and draw up a family tree of the patient that may suggest a particular pattern of inheritance. Both autosomal recessive and dominant inheritance have been reported and variable penetrance and expressivity suggest non-genetic factors to be implicated. Prenatal exposure to teratogens such as thalidomide, mycophenolate mofetil or retinoic acid, well documented as causing OAVS features, should be investigated. Additionally, smoking, diabetes and drug consumption during gestation may be interesting data to collect.

Before genome sequencing, karyotyping should be primarily considered to shed light on major chromosomal abnormalities responsible for the patient's condition. In particular, genome sequencing technologies offer great opportunities to identify genes implicated in human disorders, and have been proven useful tools for studies of syndromic forms of microtia (33).

The acquisition of data about multigenerational families with many affected patients may help in identifying causative genes. Collecting information about other families is crucial. The interaction of genetic and non-genetic factors may be responsible for the variable severity of OAVS features in these patients.

The geneticist could also give the family information on any future management decisions, as well as the foreseeable risks involved.

Although OAVS is not a progressive disease, hemifacial microsomia may become more and more evident over the years, possibly due to a more limited capacity for growth of the bone structures affected compared with those on the normal side (34).

Hemispondylus or fusion of the cervical vertebrae are common features in OAVS patients, so radiological examination of the spine is warranted. Other skeletal abnormalities are not uncommon, and thus an orthopaedic assessment can also be useful.

A lower than normal intelligence quotient (IQ) has been reported in some cases of OAVS (35), but parents may have the impression of a low IQ even when a child only has a linguistic communication delay due mainly to an inadequate management of the child's hearing loss (36).

A small number of patients may develop corneal ulcers, possibly due to impaired V cranial nerve function. An ophthalmological follow-up would be a reasonable measure when ocular abnormalities are identified or suspected.

Anomalies of the masticatory apparatus are sometimes also found. Most such problems are caused by an abnormal condyle of the temporomandibular joint, a shorter ramus of the mandible, hypoplasia/absence of the masticatory muscles, and cranial nerve

deficits. More severe malformations might be eligible for evaluation by a maxillofacial surgeon. Orthodontic assessment may be also appropriate.

A total body examination is always important as it helps to disclose abnormalities involving other organs or systems. Abdominal ultrasound is non-invasive and should be considered as the first step. If further malformations are suspected, then CT, MRI and a specialist examination may be warranted.

Conclusions

Assessing patients with microtia is not as simple as it might first appear. In most cases, ENT specialists and audiological physicians are the first to interact with a patient's family. Parents of a child with ear abnormalities are often worried about the patient's psychological development, and about the possibility of the disease progressing. Obtaining the above-mentioned information may help in such cases.

It is also very important for the family to be thoroughly informed in order to ensure their good cooperation. Accurately explaining the diagnostic process and the foreseeable risks can help parents accept the diagnosis and adjust the family's daily life to the needs of a child with hearing and possibly more extensive disabilities.

It is well known that children with hearing loss and complex disabilities have a better outcome when treated by a multidisciplinary team of specialists (37), in particular with a clinical geneticist and a neuroradiologist (38). The family must be made aware of the importance of a strict follow-up, for the normal-hearing ear as well. Speech and language therapy is also a valid option, even for patients with mild hearing loss.

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