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Rieger Syndrome: Case Report

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Abstract: Rieger syndrome is a dysembryogenetic disease in which labyrinthic damage can be associated with other genetic anomalies. The case presented here is of a patient who has bilateral dysgenesis of the iris, with bulbar atrophy and dyscoria. The patient does not present any malformation of the craniofacial structures, of the periumbilical skin, or of the skeletal bones. The case is, therefore, a variant of the Rieger syndrome labeled *Axenfeld-Rieger syndrome*. The patient reported a progressive sensation of auricular fullness, and liminal audiometry revealed a sensorineural hearing loss. Computed tomography scanning of the temporal bone revealed a bilateral dysmorphism of the acoustic channels. The presence of a bilateral cochleopathy in a patient suffering from the Axenfeld-Rieger syndrome could be the expression of a genetic "disorder." We cannot exclude the possibility also that this genetic anomaly is responsible for the bony dysmorphism of the inner ear channels shown by the computed tomography scan of the temporal bone.

Key Words: hearing loss; Rieger syndrome

Dysembryogenetic labyrinthopathies are either congenital (already present at birth) or occur subsequently in the course of years. Various classifications of these clinical forms have been proposed, but none is free from criticism.

Lyndsay [1] subdivided the structural alterations of the inner ear on the basis of the period of embryogenesis in which they appear. Three types of malformations are thus distinguished. Those of the *Michel type*, which appear during the first 3 weeks of pregnancy, are characterized by a complete block of the development of the otic capsule and nerve VIII. This is the rarest form of congenital dysplasia. The *Mondini-Alexander types* of malformation are caused by a subtotal dysplasia of the bony labyrinth or cochlear membrane. They appear about the seventh week of pregnancy and almost totally concern the cochlear labyrinth. The *Scheibe malformation* is the most frequent; it involves the membranous labyrinth at the level of the cochlear and saccular ducts and the spiral ganglion, although the bony structures of the posterior labyrinth are preserved.

Another classification of the congenital malformations of the inner ear arises from the radiological image of the bony malformations of the labyrinthic capsule. On one hand, these are the bony anomalies limited to the anterior labyrinth that, in some cases, can also be absent, although the bony structures of the posterior labyrinth appear normal or slightly altered; on the other hand, the malformations of the inner ear center on the posterior bony labyrinth, although the anterior one appears normal [2].

However, these nosologic criteria of the labyrinthic disembryopathies do not always correspond to the semeiological and clinical points of view. In fact, the results of the otoneurological tests do not always reflect correctly the functional deficit of the labyrinthic district altered by the damage. Moreover, what must be remembered is that not all the anomalies of the inner ear depend on a genetic malformation. Often they can follow pathological events that appear during germinal, embryological, or fetal life because of various etiological factors: Rh factor incompatibility or viral, toxic, dysendocrinal, or dysmetabolic diseases, and the like. For all these reasons, labeling the malformative anomalies of the inner ear with the term of *hereditary labyrinthopathies* was suggested recently, without any eziological

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or topodiagnostic reference to the damage, with the thought that this criterion of classification could better indicate the typology of these malformations. Among these clinical forms, labyrinthic damage is not generally the only anomaly. In fact, it is often associated with dysembryogenetic alterations that involve other anatomical districts as well. Thus, multiform clinical features can be observed, whether for the variability of the type or for the site of the damage.

Rieger syndrome is one of these clinical forms in which labyrinthic damage can be associated with other genetic anomalies, among the most important of which are ocular alterations. The hereditary origin of this syndrome, known since the last century (1983), was recognized by Rieger [3] in 1935. From a clinical point of view, ocular malformations are the most typical characteristic of this disease [4,5]. They involve the anterior chamber of the eye (iridogoniodysgenesis); the form and the location of the pupil (dyscoria); the number (i.e., more than one) of pupils (polycoria); and, occasionally, the lack of an iris (aniridia). Other ocular abnormalities, such as microcornea, megalocornea, corneal opacity, and strabismus, have been reported. By age 20, some 50% of affected patients present an increased intraocular pressure that tends to increase with age. Control of glaucoma is difficult, and this disorder may lead to significant damage to the optic nerve and to blindness. Another characteristic anomaly of Rieger syndrome is the presence of midfacial hypoplasia, accompanied sometimes by a cleft palate, mandibular prognathism, and a reduced number of incisors and superior and inferior premolars (hypodontia), which appear to be altered in their form [6,7]. The clinical feature is completed by the presence of skin malformations of the periumbilical area, wherein a congenital hernia may be observed in some cases. Subsequently, other dysembryogenetic skeletal alterations may appear, as may hypospadias [5], anal stenosis [8], Meckel's diverticulum, cardiac defects [9–13], leptomeningeal calcifications, and psychomotor disturbances [14–16].

Rieger syndrome is an autosomal dominant condition associated with mutations in the *PITX2* gene at chromosomes 4q25-4q26-13q14 [17–21], in the *PAX6* gene at chromosome 11 [22], and in the *FKHL7* gene at chromosome 6p25 [23].

CASE REPORT

The patient whom we have observed is a 32-year-old man (B.M.) who, from an early age, has suffered from a bilateral dysgenesis of the iris with bulbar atrophy and dyscoria. Moreover, optic atrophy is present due to glaucoma in the right eye, wherein the visual acuity is 20/100, and to a severe visual defect in the left eye, wherein the visual acuity is 20/25. The ocular pressure is high (38/47 mm Hg). At the age of 23, the patient reported a progressive sensation of auricular fullness in the left ear. The pure-tone audiogram, conducted in May 1991, revealed a sensorineural hearing loss in that ear (Fig. 1). The brainstem evoked responses demonstrated repeatable waves, with latencies of wave V within normal limits and without interaural asymmetries. A year and a half later (1993), the patient underwent another audiometric checkup: He noted a worsening of the hearing loss in the left ear, although hearing in the right ear remained normal (Fig. 2). Speech audiometry revealed an increase in the speech discrimination threshold, which reached 100 dB.

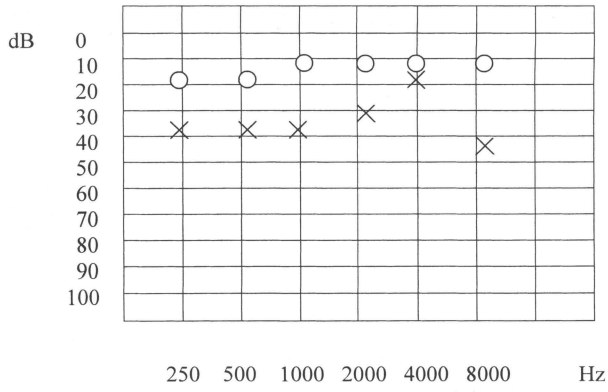

Figure 1. Pure-tone audiogram: initial sensorineural hearing loss on the left side.

Computed tomography (CT) scanning of the temporal bone disclosed a bilateral dysmorphism of the inner acoustic channels, whereas the bony structures of the labyrinthic capsule appeared to be normal (Fig. 3). Subsequent audiometric controls revealed, besides the

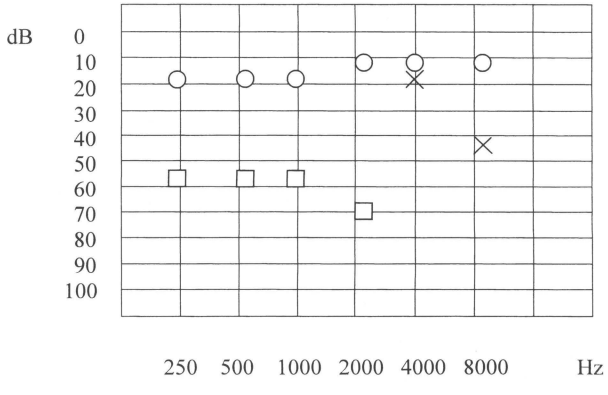

Figure 2. Pure-tone audiogram: the left hearing deficit worsened. Speech audiometry: increased threshold of discrimination in left ear.

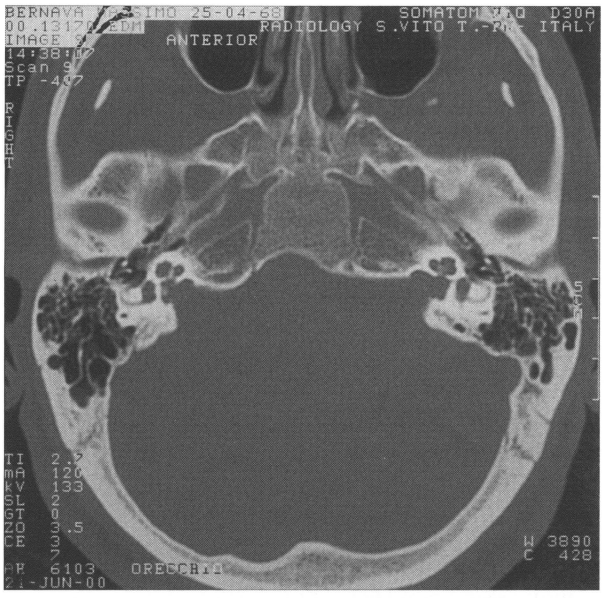

Figure 3. Computed tomography scan: bilateral dysmorphism of the inner-ear channels.

increased hearing deficit in the left ear, the presence of a sensorineural hearing loss prevalent more considerable for the low frequency in the right ear (Fig. 4). A control CT scan does not show any variation in the features reported previously.

The patient does not present any malformation of the craniofacial structures (prognathism, hypodontia), of the periumbilical skin, or of the skeletal bones. The disorder is, therefore, a variant of the Rieger syndrome. The diagnosis of Rieger syndrome, as our case demonstrates, is often complicated by the variety of dysmorphogenetic anomalies associated with ocular damage characterized mainly by iridogoniodysgenesis.

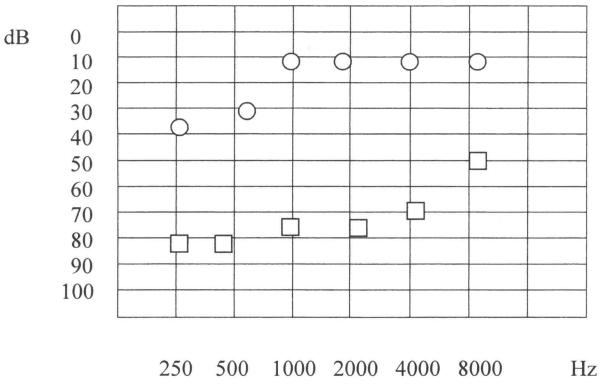

Figure 4. Pure-tone audiogram: left hearing loss further worsened; initial sensorineural hearing loss in the right ear.

DISCUSSION

Most authors agree that the typical features of Rieger syndrome involve morphogenetic anomalies of the anterior chamber of the eye, the craniofacial bones, the incisors, and the periumbilical skin. This nosologic definition does not change if, in some cases, other dysmorphogenetic alterations are associated with the main signs, rendering multiform the original features of the disease. In contrast, authors hold divergent opinions regarding definition of the clinical features in which the malformative damage involves only the anterior chamber of the eye, with consequent glaucoma and visual deficit [24]. These cases have been labeled *Axenfeld-Rieger syndrome* [25]. Our case report might reveal this syndrome. In fact, from an early age our patient has experienced ocular disturbances characterized by increased pressure and visual deficit that worsened over the course of years.

Clinical data do not prove the presence of congenital anomalies of other organs and systems. Instead, a sensorineural hearing loss is present, which started in the left ear at age 23 and progressively worsened. No vertiginous symptomatology, posture disturbance, or hypervagotonic neurovegetative symptoms were felt by the patient. Vestibular tests do not reveal any asymmetrical signs. Liminal and speech audiometry and brainstem evoked responses have confirmed the cochlear site of the damage. During subsequent years, a hearing deficit occurred in the right ear as well, with a progressive increase in the audiometric threshold for the low frequencies, as at the onset of the hearing loss in the opposite ear. In our case, therefore, the congenital ocular malformation, typical of the Axenfeld-Rieger syndrome, does not stand alone but is associated with a sensorineural hearing loss. It is, therefore, a variant of this syndrome, owing to the presence of a hearing deficit that has the characteristics of a hereditary labyrinthopathy.

Cunningham et al. [11], Moog et al. [14], Wenstrom et al. [26], and Joo et al. [27] described a hearing loss, even if rare, among the dysembryogenetic anomalies of the Axenfeld-Rieger syndrome. The presence in our patient of such a loss confirms the possible association of labyrinthic damage with the other anomalies of the hereditary origin of this syndrome. The lack of clinical signs related to the vestibular structures is not surprising, even in the presence of signs related to the cochlear labyrinth.

Today, no genetic interpretation accounts for the involvement of cochlear function in the chromosomal anomaly responsible for the Axenfeld-Rieger syndrome. Nevertheless, the presence of a bilateral cochleopathy in a patient suffering from the Axenfeld-Rieger syndrome could be the expression of a genetic

"disorder" that, as often occurs, is not limited to a specific malformative alteration but produces a variety of anomalies as expressions of more extensive chromosomal damage. We cannot exclude the possibility that this genetic anomaly is responsible also for the bony dysmorphism of the inner-ear channels shown by CT scan of the temporal bone.

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