Vestibular Function in Children With the CHARGE Association

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Background: Histopathological examinations and computed tomographic scans of the temporal bone in patients with the CHARGE association (a malformative syndrome that includes coloboma, heart disease, choanal atresia, retarded development, genital hypoplasia, and ear anomalies, including hypoplasia of the external ear and hearing loss) have shown an absence of semicircular canals and a Mondini form of cochlear dysplasia. Until recently, no information was available concerning a possible loss of vestibular function, which could be a factor in retarded posturomotor development. To our knowledge, this is the first report of otolith tests done on patients with the CHARGE association.

Objective: To test residual vestibular function in patients with the CHARGE association.

Study Design: In 7 patients with the CHARGE association, we made electro-oculographic recordings of vestibulo-ocular responses to earth-vertical and off-vertical axis rotations to evaluate the function of the canal and the otolith-vestibular systems.

Results: None of the 7 patients had semicircular canals in the computed tomographic scan, and none had canal vestibulo-ocular responses to earth-vertical axis rotation, but all had normal otolith vestibulo-ocular responses to the off-vertical axis rotation test.

Conclusions: These results support the hypothesis of a residual functional otolith organ in the hypoplastic posterior labyrinth of children with the CHARGE association. The severe delays in psychomotor development presented by these children are more likely a consequence of multiple factors: canal vestibular deficit, visual impairment, and environmental conditions (long hospital stays and breathing and feeding problems). The remaining sensitivity of the otolith system to gravity and linear acceleration forces in these children could be exploited in early education programs to improve their posturomotor development.


The CHARGE association was first described by Pagon et al1 in 1981 as an acronym for a combination of various congenital anomalies found in children who nonetheless have normal karyotypes.2 No hereditary pattern has been found. The most frequently occurring anomalies in this rare malformative syndrome are coloboma of the retina, heart defects, choanal atresia, retarded growth and development with central nervous system anomalies, genital hypoplasia, and ear anomalies that usually produce deafness. Several other anomalies have also been described, but most occur less frequently. Some authors,3,4 however, have reported a particular hypoplasia of the temporal bone that appears in most children with the CHARGE association. This is manifested by a bilateral absence of the semicircular canals with a unique remaining vesicle for the posterior labyrinth and a Mondini-type hypoplasia of the cochlea. In 1 patient,5 histopathological examination of the temporal bone revealed a unique sensory structure (according to the authors, more similar to the saccule than the utricle) at the level of the residual posterior labyrinth. We were interested in testing patients with the CHARGE association to determine whether the hypoplastic vestibules were functional because these could provide a source of vestibular information. Complete bilateral congenital vestibular deficits can cause severe delay in posturomotor development, even in the absence of other neurologic disease (S.R.W.-V., Claudia Chatelain, MD, Françoise Toupet, P.N., unpublished data, 1997-1998).7

Seven children presenting the characteristics of the CHARGE association were tested for vestibulo-ocular responses (VORs) to an earth-vertical axis rotation (EVAR) to evaluate vestibular canal func-
PATIENTS AND METHODS

SUBJECTS

Seven children with the CHARGE association (Table 1), aged 1 to 10 years, were tested to evaluate their vestibular function. The criterion for selection was that the patient had residual visual function sufficient to permit ocular pursuit of a luminous target and ocular saccades. This was required to accurately calibrate the eye movements for electro-oculographic recordings of the VORs; it is known that vision is necessary for the VORs to develop properly. Poor vision or blindness often occurs with the CHARGE syndrome because of the frequent association of coloboma.13 Visual acuity is also difficult to measure with precision in young children. All 7 children included in this study had coloboma; no precise evaluation of their visual acuity was possible, but they were all capable of precise gaze fixation and ocular pursuit of a target.

METHODS

The children were diagnosed as having the CHARGE association after a complete checkup in the pediatric departments of 2 hospitals (Robert Debre and Necker Enfants Malades) in Paris. They were referred to the otolaryngology department of the Robert Debre Hospital because of a delay in posturomotor control acquisition (a sign of a vestibular deficit) and other equilibrium problems (Table 1). All 7 children had a complete clinical otoneurologic examination and computed tomographic scans to characterize the inner ear malformations. Recordings were made of their canal and otolith VORs during EVAR and OVAR.8,9,11,12 The vertical and horizontal eye movements were recorded with lightweight adhesive electro-oculographic electrodes. Each child was seated on the lap of a parent in a special chair and the axis of rotation adjusted to the head axis of the child. Eye movements were calibrated by asking the child to fixate on a light-emitting diode lit at several positions on a black panel positioned 1.0 to 1.4 m from the child’s eyes (Figure 1). The salience of the light-emitting diodes was reinforced by juxtaposing a luminous and noisy toy that was displaced to positions of light-emitting diodes. The position of the eye with respect to a reference (gaze straight ahead) is used to correlate the recorded corneoretinal potential and the amplitude in degrees of the eye displacement. The computer-controlled rotating chair delivered the vestibular stimulation by first applying a brief acceleration, reaching a constant velocity (60°/s) rotation about the earth-vertical axis, then inclining (at a 13° tilt) the axis of rotation (this is the “rotation-tilt paradigm” described fully elsewhere.8,9,11,12) Eye movement velocity was calculated digitally using the 2-point central difference algorithm (50-millisecond steps). The quick phases were removed using an algorithm based on velocity and acceleration thresholds and systemically checked and manually corrected when necessary.

The canal vestibular function was evaluated with the canal VOR test, which measured variables that included time constant and maximal slow-phase velocity (Figure 2). Otolith VOR tests measured the modulation amplitude and the bias of the slow-phase velocity for horizontal and vertical eye movements.8,9,11,12 These data were averaged (over 10-20 cycles of rotation) according to the following formula: SP (t) = M + A cos(2π/T + j), with SP indicating slow phase velocity curve; t, time; M, the bias; A, the amplitude of the modulation of the response; cos, cosine function; T, the period of rotation; and j, the phase of the eye movements. To quantify the asymmetry of the responses between the left and right otolith systems, we calculated the directional preponderance and the relative modulation amplitude between otolith VORs obtained for right (R) and left (L) rotations (Table 2). The directional preponderance is as follows: (bias R + bias L)/2, and the relative modulation asymmetry is as follows: 100[(R modulation − L modulation)/(sum of R ± L modulations)].9,12

In previous studies,8 otolith VORs were shown to vary with age. Thus, the values obtained for patients with the CHARGE association were compared with those of 2 control groups of children—toddlers and older children—matched for age at the time of the test (Table 2) (S.R.W.-V, unpublished data, 1993-1998).11,12 The dates of milestones in posturomotor control acquisition, including head holding, sitting without support, and independent walking (ie, 3-4 steps without falling), were carefully noted for each child from their pediatric medical records. Normal ages for the acquisition of these different developmental stages have been published elsewhere.14-16

RESULTS

None of the patients with CHARGE association had semicircular canals detectable in the computed tomographic scans (Table 1). In each case, the posterior labyrinth was composed of only a unique vesicle. This is shown in Figure 3, which compares the same computed tomographic scan section of a normal 10-year-old child and a patient with CHARGE association (patient 1).

For all 7 patients, no canal VOR was measurable in response to the 40°/s2 acceleration (or deceleration) of the EVAR. This confirms recently published results from patients with CHARGE association.17,18 Otolith VORs, however, were detected in all patients during OVAR stimulation (Table 2). The mean ± SD values of the otolith VORs are in a normal range: horizontal modulation amplitude, 3.0°/s ± 1.4°/s; vertical modulation amplitude, 4.8°/s ± 3.3°/s; relative asymmetry of modulation amplitude, 24.0°/s ± 24.2°/s; horizontal directional preponderance, −0.8°/s ± 3.2°/s; and vertical directional preponderance, −2.0°/s ± 3.8°/s. The comparison of the OVAR responses between patients with CHARGE association and the control group showed no significant differences (P = .26 [Student t test], for horizontal modulation; P = .77, for vertical modulation; P = .55, for horizontal directional preponderance; and P = .65, for vertical directional pre-
Table 1. Specific Malformations Presented by 7 CHARGE Patients*

| Patient No./Sex | Heart Defects | Choanal Atresia | Genital Hypoplasia | Hearing Loss (Right/Left Thresholds), dB | CT Scan
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1/M</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>40/40; sensorineural and conductive</td>
<td>Normal cochlea</td>
</tr>
<tr>
<td>2/M</td>
<td>No</td>
<td>Unilateral</td>
<td>Yes</td>
<td>60/60; sensorineural</td>
<td>Mondini-type anomaly</td>
</tr>
<tr>
<td>3/F</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>55/60; sensorineural and conductive</td>
<td>Normal cochlea</td>
</tr>
<tr>
<td>4/M</td>
<td>Ductus arteriosus</td>
<td>No</td>
<td>No</td>
<td>60/80; sensorineural and conductive</td>
<td>Normal cochlea</td>
</tr>
<tr>
<td>5/M</td>
<td>Transposition of great vessels, atrioventricular septal defect</td>
<td>No</td>
<td>Yes</td>
<td>35/40; sensorineural</td>
<td>Mondini-type anomaly</td>
</tr>
<tr>
<td>6/M</td>
<td>Atrial septal defect</td>
<td>Bilateral, minor</td>
<td>No</td>
<td>80/100; sensorineural and conductive</td>
<td>Normal cochlea</td>
</tr>
<tr>
<td>7/M</td>
<td>Ventricular septal defect, pulmonary artery stenosis</td>
<td>No</td>
<td>No</td>
<td>60/70; sensorineural</td>
<td>Normal cochlea</td>
</tr>
</tbody>
</table>

* All patients had bilateral coloboma, retarded development, and bilateral minor external ear deformity.

† On computed tomographic (CT) scan, none of the patients had semicircular canals, and anomalies were bilateral.

Figure 1. Calibration made in a 5-month-old child. The black columns indicate the position of the eyes used for the calibration; EOG, electro-oculographic recordings before calibration on this tracer.

Otolith responses to OVAR can be found in patients with no semicircular canals and residual otolith sensorial structure. In addition, these patients have no response to EVAR.\(^\text{17,18}\)

These findings prove that the response to OVAR persists in the absence of canal responses and provide an independent evaluation of otolith function. The responses obtained to OVAR, however, could be triggered by proprioceptive receptors and otolith receptors. Although we cannot rule out completely the participation of proprioceptive inputs in the responses observed during OVAR, no such mechanism provided any OVAR response in these patients. Furthermore, complete bilateral destruction of the vestibular receptors (canal and otolith) produces abnormal responses to OVAR.\(^\text{20}\)

In our experience, OVAR responses in patients with bilateral complete vestibular deficit is always characterized by a modulation inferior to 1°/s and a zero bias in both sides (S.R.W.-V., Claudia Chatelain, MD, Françoise Toupet, P.N., unpublished data, 1997-1998), which is not the case in any of our patients with CHARGE association.

In 2 patients, the description by the child of the sensations perceived during EVAR and OVAR supported this interpretation: no sensation of movement was perceived during EVAR. This is consistent with the absence of response found for this canal stimulation. But during OVAR, a sensation of slow rotation in the direction opposite to the rotation of the chair was reported.
similar to the sensation reported during OVAR by subjects with a normal vestibular system. This suggests that otolith VOR recorded in patients with CHARGE association corresponds to a normal, or close to normal, otolith function.

Does the sensory end organ that remains in the unique otolith vesicle of patients with CHARGE association correspond to a saccule or a utricle? This question is difficult to answer because it is now known that the areas of the maculae of the saccule and utricle for these 2 types of otolith receptors (in rodents) are complex and are not simply in the horizontal plane for the utricle and the frontal plane for the saccule. It is, therefore, impossible to attribute the OVAR responses to a simple utricular stimulation. The OVAR stimulation is likely activating both the utricle and saccule. Our data show that the residual otolith organ can respond as well for translation (presumed to be simulated more by the horizontal component of the OVAR responses) as for backward-forward and vertical translation (supposed to be represented more by the vertical component of the OVAR response).

The significant delay in posturomotor development observed in all patients with CHARGE association is certainly multifactorial. This cannot be imputed only to vestibular deficits because these patients have functional otoliths. The absence of canal information during rapid head movements, however, may explain the serious equilibrium problems and frequent falls observed in these children when they make such movements. The canal vestibular deficit could well constitute a factor in the delay of their posturomotor development.
For all patients with CHARGE association, the acquisition of head holding and sitting without support was delayed compared with that in controls. Two observations (in patients 4 and 6) suggest that early stimulation of these children in an adapted program of physical therapy may facilitate their development of posturomotor control. In these patients with multifactorial causes of delayed posturomotor acquisition, it seems critical to evaluate as precisely and as early as possible the actual sensorial and motor deficits and spared functions to develop a specific physical therapy program.

CONCLUSIONS

There is a residual functional otolith organ in the hypoplastic posterior labyrinth of children with the CHARGE association. The severe delays in development presented by these children are more likely to be a consequence of multiple factors, including the canal vestibular deficit, visual impairment (due to the coloboma), other neurologic impairments, and difficult environmental conditions during the first years of life—long hospital stays, surgical procedures for cardiopathy, and breathing and feeding problems. Early and intensive physical therapy to exploit the remaining sensory information (including that from the otoliths) for each child could improve their psychomotor development.

For evaluation of the vestibular function, the slow-phase (SP) velocity of the VOR to earth-vertical axis rotation (EVAR) (providing external semicircular canal stimulation) and to off-vertical axis rotation (OVAR) (providing otolith stimulation) was measured. None of the 7 patients had canal VORs to EVAR, but they all had otolith VORs. DP indicates directional preponderance.

Table 2. Vestibulo-ocular Responses (VORs) and Milestones in the Posturomotor Development of 7 CHARGE Patients Compared With Those of Controls*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>EVAR Responses</th>
<th>OVAR Responses</th>
<th>Posturomotor Milestones, Age in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP Velocity, °/s</td>
<td>Time Constant, s</td>
<td>Horizontal Modulation, °/s</td>
<td>Vertical Modulation, °/s</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>0.0</td>
<td>1.6</td>
<td>3.4</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0.0</td>
<td>3.5</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>0.0</td>
<td>4.1</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.0</td>
<td>5.1</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0.0</td>
<td>1.9</td>
<td>7.6</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>0.0</td>
<td>1.8</td>
<td>9.6</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>0.0</td>
<td>1.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Normal</td>
<td>1 to 3 (n = 17)</td>
<td>50 ± 12</td>
<td>10 ± 1</td>
<td>6.1 ± 2.0</td>
</tr>
<tr>
<td>Controls</td>
<td>10 to 14 (n = 13)</td>
<td>42 ± 8</td>
<td>13 ± 2</td>
<td>2.2 ± 0.9</td>
</tr>
</tbody>
</table>

* For evaluation of the vestibular function, the slow-phase (SP) velocity of the VOR to earth-vertical axis rotation (EVAR) (providing external semicircular canal stimulation) and to off-vertical axis rotation (OVAR) (providing otolith stimulation) was measured. None of the 7 patients had canal VORs to EVAR, but they all had otolith VORs. DP indicates directional preponderance.

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Figure 3. Temporal bone computed tomographic scans (of comparable transversal planes) of, top, a normal 10-year-old child and, bottom, a patient with the CHARGE association (patient 1). In the normal child, the external semicircular canal is clearly visible (3), and the utricle-saccule cavity (2) is larger than the corresponding structure in the patient with the CHARGE association. The temporal bone surrounding the vestibule is also more developed in the normal child than in the patient with the CHARGE association. The numbers indicate the following structures: 1, internal auditory canal; 2, vestibular cavity; 3, semicircular canal; 4, cochlea; and 5, malleus in the middle ear cavity.
REFERENCES