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.
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. 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 Debré and Necker Enfants Malades) in Paris. They were referred to the otorhinolaryngology department of the Robert Debré 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. 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). 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 systematically 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 3). Otolith VOR tests measured the modulation amplitude and the bias of the slow-phase velocity for horizontal and vertical eye movements. These data were averaged (over 10-20 cycles of rotation) according to the following formula: 100[(R modulation − L modulation)/(sum of R ± L modulations)]9,12 These were then compared with the normal data for age and the 2 patients with CHARGE association. The directional preponderance and the relative modulation amplitude between the 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)].

In previous studies, 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). 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.

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%/s acceleration (or deceleration) of the EVAR. This confirms recently published results from patients with CHARGE association. 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*

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Heart Defects</th>
<th>Choanal Atresia</th>
<th>Genital Hypoplasia</th>
<th>Hearing Loss (Right/Left Thresholds), dB</th>
<th>CT Scan Anomalies†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>No</td>
<td>No</td>
<td>Yes</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.

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.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 EVAR response in these patients. Furthermore, complete bilateral destruction of the vestibular receptors (canal and otolith) produces abnormal responses to OVAR.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.

Figure 2. The earth-vertical axis rotation (EVAR) and off-vertical axis rotation (OVAR) techniques. The “rotation-tilt” paradigm was used for OVAR stimulation (from Denise et al, Darlot et al, and Furman et al). First the chair was rotated about the vertical axis with an initial acceleration of 40°/s² (left panel). Then, while rotation continues at a constant velocity of 60°/s, the axis was tilted by 13° with reference to gravity (right panel). The test was made in complete darkness on a computer-controlled rotating chair. Horizontal and vertical eye movements were recorded with electro-oculographic electrodes. Show phases of the eye movements for velocity measurement were selected manually and are indicated on the traces by black bands. The bottom trace of the left panel shows the absence of canal vestibulo-ocular response (absence of nystagmus) after an initial leftward acceleration in a patient with the CHARGE association. Comparison with the response in a control subject is shown in the middle trace. The lower traces of the right panel show the characteristics of the otolith vestibulo-ocular response for a left rotation: modulation of the eye movements (second and third traces) is synchronized to the position of the chair during the rotation (upper trace). The 2 graphs on the bottom show the corresponding velocities of the eye movements recorded during 12 cycles of OVAR as a function of the orientation of the chair: horizontal eye movements on the right and vertical eye movements on the left. The continuous line corresponds to the best-fitting sinusoid from which the averaged bias was calculated (for this patient, the horizontal bias was 0.26°/s ± 0.29°/s, and the vertical bias was –0.14°/s ± 0.29°/s [mean ± SD]). The mean modulation for this patient was 1.02°/s for the horizontal component and 3.52°/s for the vertical component.
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 hypoplasic 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,6,22,23 and difficult environmental conditions during the first years of life—long hospital stays, surgical procedures for cardiopathy, and breathing and feeding problems.6,22-24 Early and intensive physical therapy to exploit the remaining sensory information (including that from the otoliths) for each child could improve their psychomotor development.6,24

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REFERENCES


