Can Imaging Aid Diagnosis of Inner Ear Malformation and Predict DiGeorge Syndrome?

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Abstract

Objective: To identify congenital malformations of temporal bone and more particularly the inner ear in DiGeorge syndrome.

Methods: We conducted a retrospective study from January 2003 to December 2011 at Rouen University Hospital. Temporal bone Computed Tomography (CT) images of 13 patients with genetically confirmed DiGeorge syndrome were extracted from the database and systematically reviewed. All imaging was independently then jointly evaluated by both a senior and junior radiologist who was blinded to clinical data and audiometric findings.

Results: Review of CT images did not evidence any notable malformation of the external or middle ear. The anomalies identified correlated with the post otitis past of the patients. Conversely, we found either hypoplasia or agenesis in 69% of anomalies involving the lateral semicircular canal (LSCC). The vestibule was dilated in 31% of cases. There was no correlation between sensorineural hearing loss (SNHL) and the labyrinthine anomalies described.

Conclusion: In the present study, CT imaging was able to identify frequent malformation of the inner ear in DiGeorge syndrome, i.e., hypoplasia or agenesis of the LSCC, without referring to audiometric findings. Moreover, the fortuitous diagnosis of this kind of malformation by CT scan performed for other investigations may lead to suspect Di George syndrome (22q11 deletion) moreover if other symptoms are associated.

Keywords: DiGeorge syndrome; Inner ear malformation; Lateral semicircular dysplasia; Sensorineural hearing loss

Abbreviations: FISH: Fluorescence In Situ Hybridization; IVC: Interventricular Communication; IAC: Interauricular Communication; PFO: Patent Foramen Oval; CHL: Conductive Hearing Loss; SNHL: Sensorineural Hearing Loss; CT: Computed Tomography; SCC: Semicircular canal; LSCC: Lateral Semicircular Canal; PSCC: Posterior Semicircular Canal

Introduction

DiGeorge or 22q11 deletion syndrome was first described in 1965. It is a genetic syndrome characterized by deletion of band 11 on the long arm of chromosome 22. The term CATCH 22 has been employed (Cardiac anomaly, abnormal face, thymus hypoplasia, cleft palate, hypocalcemia, chromosome 22) but fails to describe all the anomalies.

In 1981, a direct link was established between chromosome 22 deletion and manifestations of 22q11 syndrome. Early diagnosis is mandatory to prevent possible cardiac complications and to recognize and treat any neurosensory deficits in childhood, which may negatively impact a child’s psychomotor development.

To date, the literature has focused on conductive hearing loss (CHL), secondary most of the time to media otitis related to velopharyngeal insufficiency, but no anatomical correlation has been found with SNHL [1-3]. Thus, the objective of this present study was to identify inner ear anomalies by computed tomography (CT) imaging and to compare with audiometric findings.

Materials and Methods

Study population

The present study was conducted between January 2003 and December 2011 at Rouen University Hospital and involved pediatric radiologists and otolaryngologists. This study was approved by the Ethics Review Committee of our institution. We retrospectively assessed the temporal bone CT images of 13 patients with genetically confirmed DiGeorge syndrome and who presented hearing loss.

Patient age ranged from 1 to 15 years and mean age was 9.6 years. There were 10 girls and 3 boys. All clinical history including audiometric findings and temporal bone CT imaging was available for all patients.

CT protocol and imaging analysis

Two neuroradiologists blinded to the clinical findings (a senior physician specialized in pediatric head and neck radiology and a final year resident at the end of his specialty training) reviewed CT imaging (GE light speed 16, 120 Kv, 120 mA, thickness 0.3 mm).

A key for reading temporal bone CT was pre-established, then applied from one patient to another, using superposable measures referenced in the literature [4-12].

Thus, CT analysis was always performed by listing and analyzing the following items:

• External auditory canal.

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• Ossicular chain, footplate of the stapes, distance between crura of stapes using oblique multiplanar reformation in stapes axial plane.
• Lateral semi-circular canal (LSCC). It was considered as dilated when the anterior limb was >1.8 mm and posterior limb >1.7 mm and as shortened when the length was less than 4 mm.
• Measurement of the bony island area. It was considered as hypoplastic when the area was less than 7 mm².
• The vestibule was considered as dilated when the width was more than 3.5 mm [10,11].
• Cochlea: height less than 3.5 mm in coronal plane.
• The vestibular aqueduct was considered dilated when the diameter of its medium section was superior to the diameter of the posterior semi-circular canal or >1.5 mm.
• The following clinical findings were documented:
  • Pure-tone audiometry taking into account hearing loss of more than 20 dB and the difference between conductive and sensorineural hearing loss. For two of the patients, audiometric recording was suggested since we were unable to perform audiometry (agitated children).
  • Endocrinology anomalies: hypocalcemia, thyroid disorders (Table 1).
  • Cardiac anomalies (Table 1).
  • Head and neck anomalies (Table 2).

Results

Inner ear malformation was observed in 9 (69%) of the overall 13 patients. LSCC was involved in all 9 of these patients with 2 cases of agenesis and 7 cases of hypoplasia (Figures 1). For patients 2 and 3, the vestibule appeared dilated in association with LSCC hypoplasia (Figure 2). In 4 of the overall 13 patients, the vestibule appeared dilated in association with LSCC agenesis. Cochlea and vestibular aqueduct were normal in all patients.

Only 4 patients (4/13) had SNHL demonstrated by audiometry. In 3 of these 4 patients inner ear malformation was also found on CT. In 2 of these 4 patients, measurement of SNHL was below 20 dB, hence minimal. Patient 5 had bilateral SNHL but no inner ear malformation

| Patients | Audiometry | Velopharyngeal insufficiency | laryngotracheal anomalies |
|----------|------------|-----------------------------|---------------------------|
| 1        | CHL        | +                           |                           |
| 2        | CHL        | +                           | Epiglottitis agenesis     |
| 3        | Mixed hearing loss | +                       | Laryngeal malformation   |
| 4        | CHL        | +                           | Laryngeal malformation   |
| 5        | SNHL       | +                           |                           |
| 6        | Mixed hearing loss | +                      | Laryngeal malformation   |
| 7        | CHL        | +                           | -                         |
| 8        | CHL        | +                           | -                         |
| 9        | CHL        | +                           | -                         |
| 10       | CHL        | +                           | -                         |
| 11       | CHL        | +                           | -                         |
| 12       | CHL        | +                           | -                         |
| 13       | Mixed hearing loss | +                      | Laryngeal malformation   |

Table 2: Main head and neck anomalies related to 22q11 deletion syndrome.

![Figure 1: Right temporal bone CT in axial plane shows a hypoplasia of the LSCC with a bony island <7 mm². The vestibule appears normal.](image1)

![Figure 2: Right temporal bone CT in axial plane shows a dilatation of the vestibule (width >3.5 mm) and a LSCC hypoplasia (bony island <7 mm²).](image2)
Adkins and Gussen [21] reported a case with a narrow external auditory canal, a shortened cochlea (Mondini dysplasia) and a normal vestibular system. Weinberg and Wright [22] reported a case with isolated stapes malformation but normal inner ears. Black et al. [23] reported a case with external ear (microtia and atresia of the external canals), middle ear (absence of ossicles, stapedial muscle and oval window, hypoplasia middle ear and facial nerve) and inner ear malformations (hypoplastic cochlea with Mondini deformation and malformation of the vestibule and absence of LSCC). Othani and Schukneccht [24] reported 3 cases with various anomalies but Mondini dysplasia and LSCC involvement (wide and communicating with the vestibule) was present in all 3 cases.

Indeed, the literature is more interested in CHL than SNHL. We believe we may be the first to report inner ear malformation found on CT [1,2,13,14] thus filling a gap in the knowledge. The three SCCs are formed during the fourth to seventh embryonal periods. Any problems during the growth process may affect the proper formation of the organs. SSCC is the first to form, followed by PSCC and then LSCC. For this reason, the LSCC is likely to be particularly vulnerable and frequently malformed. Indeed, CT findings may enable early diagnosis thus helping to prevent possible cardiac complications and treat any neurosensory deficits early on in childhood.

According to the literature, 15% of patients with DiGeorge syndrome have SNHL [3]. LSCC malformation does not seem to correlate with audiometric findings. In their recent paper, Johnson and Lalwani [25] found a correlation between LSCC malformation and SNHL in 15 patients but in fact only 2 of 15 patients had an isolated LSCC malformation and no hearing loss was noticed.

The following two recent articles found no correlation between an isolated LSCC malformation and SNHL. Dallan et al. [26] reported a case of a 38 year old European man with recurrent vertigo but no hearing impairment and bilateral dilatation of the vestibule involving both the LSCC and the utricle. Yamashita et al. [27] retrospectively reviewed the CT images of 136 temporal bones (68 patients) and found no correlation between LSCC bone island width or cross-sectional area and hearing level.

To date, there are no radiological reports in the literature on aplasia of the LSCC in association with DiGeorge syndrome. This present study may help to fill a gap in the knowledge. Notwithstanding, our study is limited by the low number of patients (n=16), which may be explained by the rarity of this syndrome with a prevalence of 1 in 5000.

In this present study, CT found anomalies of the inner ear to be frequent in patients with DiGeorge syndrome. Indeed, temporal bone CT findings may sometimes enable geneticists to search for 22q11 deletion and thus suspect a diagnosis of DiGeorge syndrome. Faced with atypical dysmorphism we may hesitate between a diagnosis of CHARGE syndrome [28,29] and DiGeorge syndrome. Although Waardenburg syndrome type 2 [30] presents similar inner ear malformation to DiGeorge syndrome, aplasia of the posterior and lateral semi-circular canals prevails in the former. Clinical evaluation enables more accurate diagnosis.

CHARGE syndrome associates coloboma (eye malformation), cardiac malformation, choanal atresia, delay in growth, and genital hypoplasia, as well as anomalies of the inner ear. The inner ear anomalies most often listed involve the lateral and anterior semi-circular canal associated with absence of oval window and the footplate of the stapes [28,29]. The difference between CHARGE syndrome and DiGeorge syndrome.

| Patients | Audiometry | CT               |
|----------|------------|------------------|
| 1        | CHL        | LSCC hypoplasia  |
| 2        | CHL        | LSCC hypoplasia  |
| 3        | Mixed hearing loss | LSCC hypoplasia |
| 4        | CHL        | Normal           |
| 5        | SNHL       | Normal           |
| 6        | Mixed hearing loss | LSCC hypoplasia |
| 7        | CHL        | LSCC hypoplasia  |
| 8        | CHL        | Normal           |
| 9        | CHL        | Normal           |
| 10       | CHL        | LSCC agenesia    |
| 11       | CHL        | LSCC hypoplasia  |
| 12       | CHL        | LSCC agenesia    |
| 13       | Mixed hearing loss | LSCC hypoplasia |

Table 3: Audiometric and CT findings.

Discussion

Di George syndrome is a genetic syndrome characterized by deletion of band 11 on the long arm of chromosome 22. Microdeletion of 22q11 is sought by Fluorescence in situ hybridization (FISH) technique.

If clinical findings play an important part in diagnosis of DiGeorge syndrome [1,2,13,14], cyogenetic and molecular techniques are essential to demonstrate chromosomal abnormality and deletion of 22q11 [15-17]. This microdeletion affects the long arm and is of autosomal dominant transmission with a wide phenotypic spectrum. Recently [18,19], a link was established between an anomaly on gene TBX1 and anomalies found in DiGeorge syndrome. TBX1 seems to be a regulator controlling the differentiation and direction of posterior neural crest cells [18,19]. TBX1 is essential for normal development of hearing and enables demonstration of phenotypic dysmorphism as well as anomalies of the inner ear.

In new-born, 1 in 5000 is concerned and 5% of infants with cardiac malformation have this genetic anomaly [1]. Whereas facial malformations are common, congenital heart disease, head and neck malformation, psychomotor and language delay, as well as hypoparathyroidism are scarcer.

Head and neck anomalies and especially velopharyngeal insufficiency are present most of the time and sometimes reveal this syndrome. Laryngotracheal anomalies are relatively common and important to acknowledge, especially if cardiac surgery is planned [2,13,20]. There are few existing publications on ear malformations.

In the present study, the anomalies identified involved the middle ear and were most probably related to chronic otitis in children subject to media otitis connected to the weak aeration of the middle ear due to velopharyngeal insufficiency. The ossicular anomalies found were not significant and thus of little scientific value. These post otitis anomalies were connected with CHL. Concerning anomalies of the external ear, 3 patients (3/16) had atresia of the external auditory canals. Moreover this anomaly is little described in the literature, perhaps because such data is subjective or not mentioned in clinical observations because there is no functional deficit.

was observed. There was no relation between CT and SNHL. Only 2 patients presented agenesia of LSCC, reinforcing the absence of correlation with anomaly of the inner ear (Table 3).

Concerning anomalies of the external ear, 3 patients (3/13) had atresia of the external auditory canals.
syndrome is that in the latter, the anomaly affects all the canals. This latter facilitates differentiation between DiGeorge syndrome, which to our knowledge affects only the LSCC and agenesis or hypoplasia.

Conclusion

In spite of the low number of patients, we were able to highlight frequent anomalies (69%) of the posterior labyrinth. These anomalies do not seem to correlate with audiometric findings but may be of intellectual interest and sometimes enable diagnoses in contentious cases. To our knowledge, this is the first time that this inner ear anomaly has been reported in the radiological literature.

Moreover, the diagnosis of this kind of frequent malformation by CT scan may lead to high suspicion of DiGeorge syndrome when associated with cardiac, head and neck and endocrinologic malformations.

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