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Cochlear implant outcomes and genetic mutations in children with ear and brain anomalies

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INDICE

ABSTRACT

Introduction. Cochlear implantation (CI) was a significant surgical innovation in the 20th century and represented the first artificial sensory organ that was applied in clinical medicine. Currently, CI is still one of the most effective medical procedures. Nonetheless, cochlear implantation in adults and children represents a controversial issue from an economic, clinical and ethical point of view, especially in specific clinical conditions that could compromise the CI outcome and drastically reduce the chance of an acceptable development of perceptual and linguistic capabilities. These conditions should certainly include the presence of inner ear malformations or brain abnormalities.

Objectives. The aims of this work were to study the diagnostic value of high resolution computed tomography (HRCT) and magnetic resonance imaging (MRI) in children with sensorineural hearing loss who were candidates for cochlear implants and to analyse the anatomic abnormalities of the ear and brain in patients who underwent cochlear implantation. We analysed the effects of ear malformations and brain anomalies on the CI outcomes. Finally, we described the genetic mutations that we found in the study group. A control study group of implanted patients without ear and brain anomalies was obtained (virtually) from clinical and literature data for statistical purposes.

Materials and methods. The present study is a retrospective observational review of cochlear implant outcomes among hearing-impaired children who presented ear and/or brain anomalies at neuroimaging investigations with MRI and HRCT. Furthermore, genetic results from molecular genetic investigations (*GJB2*/*GJB6* and, additionally, in selected cases, *SLC26A4* or *mitochondrial-DNA* mutations*)* on this study group were herein described. Longitudinal and cross-sectional analysis was conducted using statistical tests.

Results. Between 1 January 1996 and 1 April 2012 at the ENT-Audiology Department of the University Hospital of Ferrara, 620 cochlear implantations were performed. There were 426

implanted children at the time of the present study (who were <18 years). Among these, 143 patients (64 females and 79 males) presented ear and/or brain anomalies/lesions/malformations at neuroimaging investigations with MRI and HRCT. The age of the main study group (143 implanted children) ranged from 9 months and 16 years (average = 4.4; median = 3.0). The most common inner ear malformation is represented by an enlarged vestibular aqueduct; brain lesions are usually represented by white matter disorders. The 35delG in the *GJB2* gene remain the most common mutation.

Discussion and Conclusions. Good outcomes with cochlear implants are possible in patients who present with inner ear or brain abnormalities, even if central nervous system anomalies represent a negative prognostic factor that is made worse by the concomitant presence of cochlear malformations. Common cavity and stenosis of the internal auditory canal (less than 2 mm) are negative prognostic factors even if brain lesions are absent.

Because the cochlear implantation is an invasive and expensive surgical procedure, the identification of predictive factors, even in hearing-impaired patients with cochlear and brain anomalies, is one of the most important goals, because it can help to guide rehabilitation programs that are tailored to meet the expectations of clinicians, teachers and parents. Our findings suggest that cochlear implantation (CI) is a safe and effective procedure even for patients with brain and inner ear abnormalities. Nonetheless, specific conditions, such as a common cavity, or in general, the absence of modiolus and the stenosis of the internal auditory canal, can increase the risk of post-operative complications and prevent the achievement of acceptable perceptual categories. For the aforementioned conditions, it is strictly recommended that cochlear implant indications, neuroimaging and surgery are performed in experienced hospitals.

Keywords: inner ear malformations, brain abnormalities, cochlear implantation, neuroimaging, *GJB2* mutations.

1. INTRODUCTION

Cochlear implant (CI) was a significant surgical innovation in the 20th century and represented the first artificial sensory organ applied in clinical medicine. Currently, CI is still one of the most effective medical procedures. It can evoke acoustic sensations by electrically stimulating the inner ear [1]. Nonetheless, cochlear implantation in adults and children represent a controversial issue from an economic, clinical and ethical point of view. The U.S. Food and Drug Administration (FDA) approved the use of cochlear implants as an auditory rehabilitation procedure in adults in 1984. Six years later, in 1990, the FDA approved cochlear implants also for children who were affected by severe-to-profound bilateral sensorineural hearing loss (with a tonal hearing threshold that is major, or equal to 90 dB nHL decibel normal hearing level, in the better ear), who were at least 1 year of age and who also did not have the benefit of adequate auditory training (typically from 4 to 6 months) with hearing-aid amplification (http://www.fda.gov/cdrh/cochlear/). A similar position was taken in 2007 in a statement of the Joint Committee on Infant Hearing, which noted that *"Cochlear implantation should be given careful consideration for any child who appears to receive a limited benefit from a trial with appropriately fitted hearing aids. Infants with profound bilateral hearing loss are candidates for cochlear implantation at 12 months of age, and children with bilateral severe hearing loss are eligible at 24 months of age. The presence of developmental conditions (e.g., developmental delay, autism) in addition to hearing loss should not, as a rule, preclude the consideration of cochlear implantation for an infant or a child who is deaf"* [2]. According to the U.S. Food and Drug Administration (FDA), as of December 2010, approximately 219,000 people worldwide have received cochlear implants [3]. Currently, there are three major FDA and EC (European Community) approved cochlear implant providers that are commonly used: Cochlear Ltd (Australia), Advanced Bionics (USA) and Med-El (Austria). The Neurelec's devices (MXM – Neurelec

Corp, Vallauris, France) have not yet been approved by the FDA, but they have a CE registration and are currently used in Europe. All of the product devices comprise similar component parts: 1) an external unit, called a transmitter or processor, which constitutes a microphone, speech processor and batteries to drive the system; 2) an implanted device, called a receiver or stimulator, which can electrically stimulate the inner ear through an electrode array inserted into the cochlea. *"The implant converts acoustic sound to electrical pulses that stimulate the auditory nerve. Acoustic input enters the microphone, which is worn on the ear, and is sent to the speech processor for analysis of intensity in a number of set frequency bands. The resulting information is sent from the externally worn transmitting coil to the subcutaneous receiver–stimulator through FM waves. These components are held together by a pair of magnets so that they are separated only by the thickness of the skin flap. Each frequency band is assigned to a particular electrode along the implanted array (mimicking the normal basal-to-apical organization of high to low frequencies in the cochlea). If instructed, this array will provide a biphasic electrical pulse to stimulate the auditory nerve. The magnitude of the pulse provided by any one electrode will depend on the acoustic intensity within the assigned frequency band and the dynamic range of current (minimum to maximum) programmed for that electrode"* [4] (Fig. 1). The design of the electrode array must incorporate biocompatibility, mechanical stability and practical fabrication and must minimise insertion trauma. From a surgical point of view, efforts to reduce the insertion trauma must be accomplished at the materials and design levels as well as through the surgical technique. The CI has been devised to allow full access to verbal communication, through the perception of phonetic hallmarks. The success of this method is then given in general by the achievement of verbal communication performance by improving the skills of verbal perception, to become comparable to people with normal hearing. In the paediatric population, in children with profound hearing loss, which is

unsuitable for obtaining significant results with traditional hearing aids, CI (if performed early) allows the optimal development of auditory and linguistic abilities, which drives toward adequate communication and intellectual development.

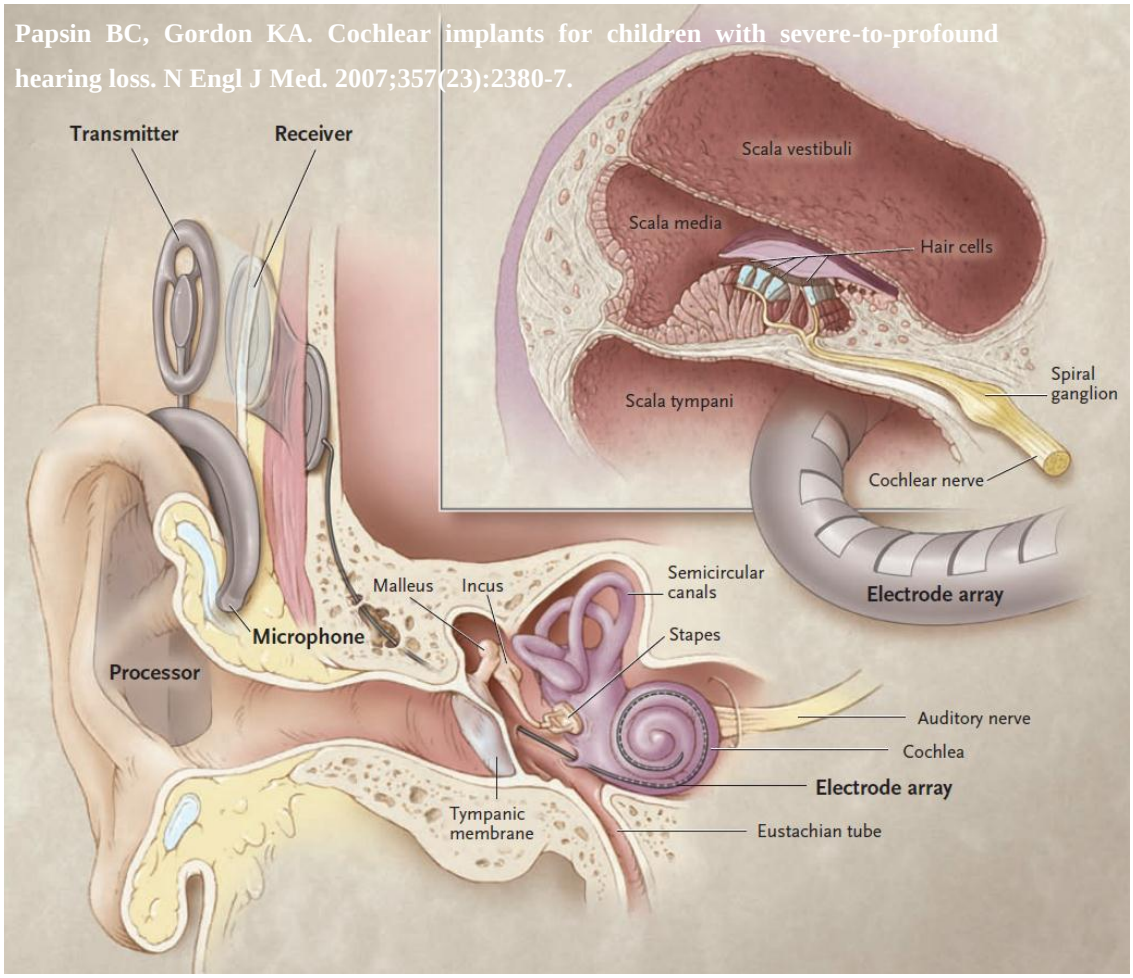


Fig. 1 - The internal (receiver) and external (transmitter) components of a cochlear implant. "The cross section of the cochlea shows the electrode array surgically placed in the scala tympani. The implant converts acoustic sound to electrical pulses that stimulate the auditory nerve. Acoustic input enters the microphone, which is worn on the ear, and is sent to the speech processor for analysis of intensity in a number of set frequency bands. The resulting information is sent from the externally worn transmitting coil to the subcutaneous receiver–stimulator through FM waves. These components are held together by a pair of magnets so that they are separated only by the thickness of the skin flap. Each frequency band is assigned to a particular electrode along the implanted array (mimicking the normal basal-to-apical organisation of high to low frequencies in the cochlea). If instructed, this array will provide a biphasic electrical pulse to stimulate the auditory nerve. The magnitude of the pulse provided by any one electrode will depend on the acoustic intensity within the assigned frequency band and the dynamic range of current (minimum to maximum) programmed for that electrode" [4].

On the other hand, the overall results of the cochlear implantation should not ignore the specific or unique conditions of the patients. It is known that auditory deprivation genres, first, have disadvantages in communication and reduction of daily activities that are closely

related to hearing impairment, and second, over time, involves other areas of personal life, leading in some cases to permanent deficits. For example, children with congenital profound hearing loss accumulate disadvantages over time in language skills and certain learning areas, which can lead to permanent limitations of personal skills at a later age. Because of the auditory habilitation/rehabilitation training with a cochlear implant, most of these patients can reach a complete disability "compensation". The effectiveness of CIs in adults and children is demonstrated by many contributions in the medical literature. Specifically, several studies have reported the results of the development of auditory perceptual and expressive verbal abilities in children with pre-, peri- and post-lingual deafness. Clinical experiences across the world have also shown that, among children with pre-verbal onset hearing loss, there is a critical period for the development of language skills, presumably due to the underlying neuronal plasticity, and learning would be strictly dependent on the presence of an adequate auditory input, which explains the need for early intervention to prevent the occurrence of a delay in language development and perceptive or expressive skills. A multi-centre study that was conducted on a large number of cases [5] showed that the majority of patients who were implanted reached the performance of verbal recognition more or less quickly depending on the age at the time of the implant surgery.

The performance of the patients who received CIs varies significantly as a consequence of a substantial number of audiological and extra-audiological factors (age of hearing loss onset, duration of auditory deprivation, auditory function residuals, presence of associated disability and comorbidity, language skills at the time of the CI, duration of CI use, the presence of certain malformations of the inner ear, socio-economic status and familial environment) [6-13]. Even if a unique prediction of the results after CI is not yet available, mostly because of the extreme heterogeneity in the aetiology among profound hearing-impaired patients, there are many prognostic factors that can contribute to the audiological

assessment. Among these, we emphasise the importance of inner malformations and brain anomalies, which are a part of the present study.

Because cochlear implantation is an invasive and expensive surgical procedure, the identification of predictive factors is one of the most important goals; knowledge of the predictive factors can help to guide rehabilitation programs that are tailored to meet the expectations of clinicians, teachers and parents. The perceptual performance improves rather quickly if the selection criteria are correct. In agreement with research in the literature, the majority of patients who received a CI at our clinic have shown a rapid advancement in their perceptual abilities, reaching the 6^{th} perceptive category according to the Geers and Moog classification one year after surgery [14]. The perception of verbal sounds is an important starting point to activate the processes of linguistic acquisition. The development of language depends on auditory skills and maturation of cortical functions (memory, attention, intellectual abilities). The linguistic processes typically follow the perceptive processes with a variable latency, which appears to be related to the age of the patients at the time of surgery [15,16]. Specifically, children implanted in a very early age (8-12 months) experience linguistic evolution with a speed that is higher than that of normal hearing children of the same age, probably because of using lines of development in various linguistic domains that are different from the usual capabilities of normal hearing children. In other words, congenitally deaf patients develop many abilities to reach an adequate communication condition (lip-reading, visual reinforcement) that, when auditory function has recovered, work in synergy with auditory inputs, enhancing perceptual and visual skills; an analogous process is similar in visually impaired patients who develop, more than normal, auditory and olfactory skills. On the other hand, it cannot be excluded that the normal auditory input is more detailed and complex and, thus, that it takes more time to develop and

integrate superior central functions. In contrast, cochlear implant stimuli are simpler; thus, they do not need complex integration in the corpus callosum or cortical areas.

With the advances in molecular genetics over the past 20 years, our understanding of the pathogenesis of sensorineural hearing loss has greatly increased. To date, more than 400 syndromes have been described in which hearing loss is a regular or occasional feature [17] and, after more than two decades of molecular biological analysis, approximately 95 non-syndromic recessive and 64 non-syndromic dominant loci have been identified [18], even if not all of them have led to the identification of specific genes. The most common mutations that are responsible for hearing loss involve the *GJB2* gene; *SLC26A4* mutations are the second cause of genetic hearing loss and the first among syndromic deafness. The *SLC26A4* (*PDS*) gene mutations result in abnormalities of the endolymphatic system, which lead to the dilation of the vestibular aqueduct as seen in Pendred syndrome. Nonetheless, other genes can be involved: normal expression of the *PAX2* and *PAX3* genes is necessary for the normal development of the cochlea. The *FGF3* gene appears to be necessary for differentiation within the otic vesicle. The *EYA1* gene has an important role in encoding transcription factors and mutations of *EYA1* are responsible for EYA1-related disorders that include BOR (branchio-oto-renal) syndrome, BO (branchio-otic) syndrome and OFC (oto-facio-cervical) syndrome [19]. Several studies have shown that patients who have mutations of *GJB2* (or Cx26) (OMIM * 121011) usually have excellent perception of speech and an optimal language development after the cochlear implant [20,21]. Additionally, it has been reported that *GJB2* mutations are not usually accompanied by macroscopic inner ear malformations. Nevertheless, there is no evidence that genetic mutations or the interaction of a genetic diagnosis with other prognostic factors (such as abnormalities of the ear and brain) can predict CI outcomes.

Therefore, pre-operative neuroimaging is mandatory in cochlear implant candidates for diagnostic and surgical purposes. This step usually includes an MRI as well a high-resolution computed tomography (HRCT) of the temporal bone. MRI should be performed with contrast (gadolinium), unless otherwise noted or unless the test is in children who are not believed to have lesions that require contrast to be diagnosed. HRCT of the temporal bone does not require iodine contrast. Note that Magnetic Resonance Imaging (MRI) is relatively contraindicated after cochlear implantation or it is arguably possible. Various experimental studies have shown that MRI scans can safely be performed with the CI in place [22,23]. This arrangement does not imply that it is generally safe to perform MRI in CI patients, because the type of implant, fixation method and MRI units and sequences could vary. Even if it can be performed safely, the distortion that is caused by the implanted magnet will cause sub-optimal interpretations [22]. For the aforementioned reasons, cochlear implantation can be contraindicated in patients who need periodic follow-up with MRI.

At our clinic, pre-operative radiological imaging of cochlear implant candidates includes both HRCT and MRI of the temporal bone during the same session, during anaesthesia, if required, which usually occurs in children. In addition to the MRI of the inner ear, we also perform brain and brainstem MRI scans. These scans enable us to exclude any incidental brain abnormalities that can contraindicate CI surgery. MRI is the best diagnostic tool for detecting malformations such as cochlear nerve hypoplasia or aplasia, and it is the best screening tool for early cochlear ossification following bacterial meningitis [24-26]. HRCT provides better images and definition of the facial nerve canal, middle ear and otic capsule [27]. Central nervous system findings have been reported in 20–40% of the patients [25-29]. Some of these findings could result in neurodevelopmental delay and could negatively impact the outcome of cochlear implantation [30]. Nonetheless, increased experience in cochlear implantation has led to more children with abnormal cochleovestibular anatomy

being considered as candidates [12]. According to the literature, approximately 20% of the children who have sensorineural hearing loss have associated radiological anomalies of the temporal bone [31-33]. These temporal bone anomalies are accompanied by a wide range of hearing acuity, varying degrees of progression of hearing loss, and the presence or absence of related non-otological anomalies [33].

The first cochlear implants in children with inner ear malformations were performed in the late 1980's [33]. Since this time, cochlear implants have been fully described and surgical techniques have been tested; precautions have been identified that are necessary to prevent or remedy possible complications. Additionally, different electrode arrays have been developed that allow a choice of the most suitable array for the different types of malformations [13,34-39]. In general, "*cochlear implantation is a relatively safe procedure with a low complication rate that ranges from 6% to 20%. Major complications are those that are life-threatening or require surgery, whereas minor complications are those that can be medically treated. The inner ear malformations can increase the risk of meningitis, cerebro-spinal fluid leakage and facial nerve palsy*" [40,41]. We should note that *"the rate of postoperative complications was higher in patients with anomalous inner ears than in patients with normal inner ears, most were minor and could be managed conservatively. These findings suggest that cochlear implantation (CI) is safe even for patients with anomalous inner ears in experienced hospitals"* [41]. Nevertheless, the functional results reached by these children (perceptual and linguistic performance) are still poorly described and have not been predictable. Case studies have limited conclusions because of the high inter-individual variability. For these reasons, it is not yet possible to draw clear guidance from the literature on which to base the selection of candidates [12,13,41]. The malformations in fact allow the correct insertion of a number of electrodes that are usually sufficient, and the patterns of neural responses are adequate to accomplish the recognition of

an open set words. However, specific conditions that prevent a correct coupling between the electrode array and the cochlear nerve, even if the latter is present, such as a common cavity, are usually characterised by a poor outcome, unless very specific surgical strategies are enacted.

1.1 Classification of inner ear abnormalities

Approximately 80% of the children who have a congenital hearing loss have no macroscopic abnormalities of the ear, and their hearing loss is assumed to be the result of dysfunctions at a cellular level in the membranous inner ear. The remaining 20% can present inner ear dysplasia, which can be demonstrated on high-quality neuroimaging (HRCT without contrast and MRI, with contrast in adults or in specific cases). The inner ear abnormalities, whether dysplastic or nondysplastic, can be isolated or can be part of a multi-organ syndrome [19]. In considering the problems specific to implanting children with ear malformations, it is valuable to consider the normal development of the inner ear. "*During the third week after conception, the otic placode appears on the surface ectoderm. This becomes invaginated to form the otic pit and, in turn, the otic vesicle or otocyst by the end of the fourth week. The vesicle divides into a ventral component, which gives rise to the saccule and the cochlear duct, and a dorsal component, which forms the utricle, semicircular canals, and endolymphatic duct. In the sixth week, the saccule forms a tubular outpocketing at its lower pole, the cochlear duct. This penetrates the surrounding mesenchyme and by the end of the eighth week has completed 21.2 turns. In the 10th week, vacuolisation in the surrounding mesenchyme around the cochlear duct forms the scala tympani and vestibuli, and following that membranous structures such as the organ of Corti begin to develop in the cochlea. The semicircular canals appear as outpocketings of the utricle about the sixth week. The central portions of these outpocketings eventually become opposed to each other and*

disappear giving rise to the three semicircular canals. The endolymphatic sac and duct is initially a wide structure, but the proximal portion, the duct narrows about the seventh week. If there is no developmental arrest before the eighth week, a normal cochlea is formed [24]. *The statoacoustic ganglion forms from neural crest cells and cells derived from the otic vesicle. It subsequently splits into cochlear and vestibular components, the spiral ganglion and Scarpa's ganglion*. *There is increasing interest in the genetic and molecular factors that drive this complicated process* [19].

In considering the specific problems for the implant of children with deafness associated with inner ear malformations, it is worthwhile to consider the normal anatomy of the inner ear (Fig. 2). The cochlea has a discrete anatomical variability in its shape and dimensions, as reported by several authors [42-48]. In humans, *"cochleae are mirror-shaped, fluidfilled, coiled, fairly symmetrical bony tubes (3.2–4.2 cm long) situated in the petrous pyramids of the temporal bones. Cochlea is composed of ~2 and three-fourth turns. The outer cochlear wall had a mean length of 42.0 mm while the first turn was 22.6 mm (range, 20.3–24.3 mm) representing 53% of the total length. The total height of the cochlea can vary from 4.4 to 5.9 mm (mean 5.1 mm). The large variations in cochlear lengths, angles between turns, and position in the skull base can influence the straightforwardness for the insertion of a CI electrode particularly passing the first turn. Most frequently damaged are the spiral ligament at the junction of the first and second half of the first turn, basilar membrane (BM), and osseous spiral lamina"* [48]. *"The average LSCC (lateral semicircular canal) bony island width is 3.7 mm (normal range, 2.6-4.8 mm). Cochlear hypoplasia (< 4.4 mm) had a positive predictive value of 100% for SNHL, whereas cochlear hyperplasia and bony island dysplasia were less predictive"* [44].

Developmental malformations that affect the otic capsule result in anomalies of both the membranous and bony labyrinth. The specific timing of the insult during otic capsule

development determines the resulting type of malformation along a spectrum of congenital inner ear malformations that can occur when the normal process of development is impacted, even if it is not necessarily understood why this result occurs.

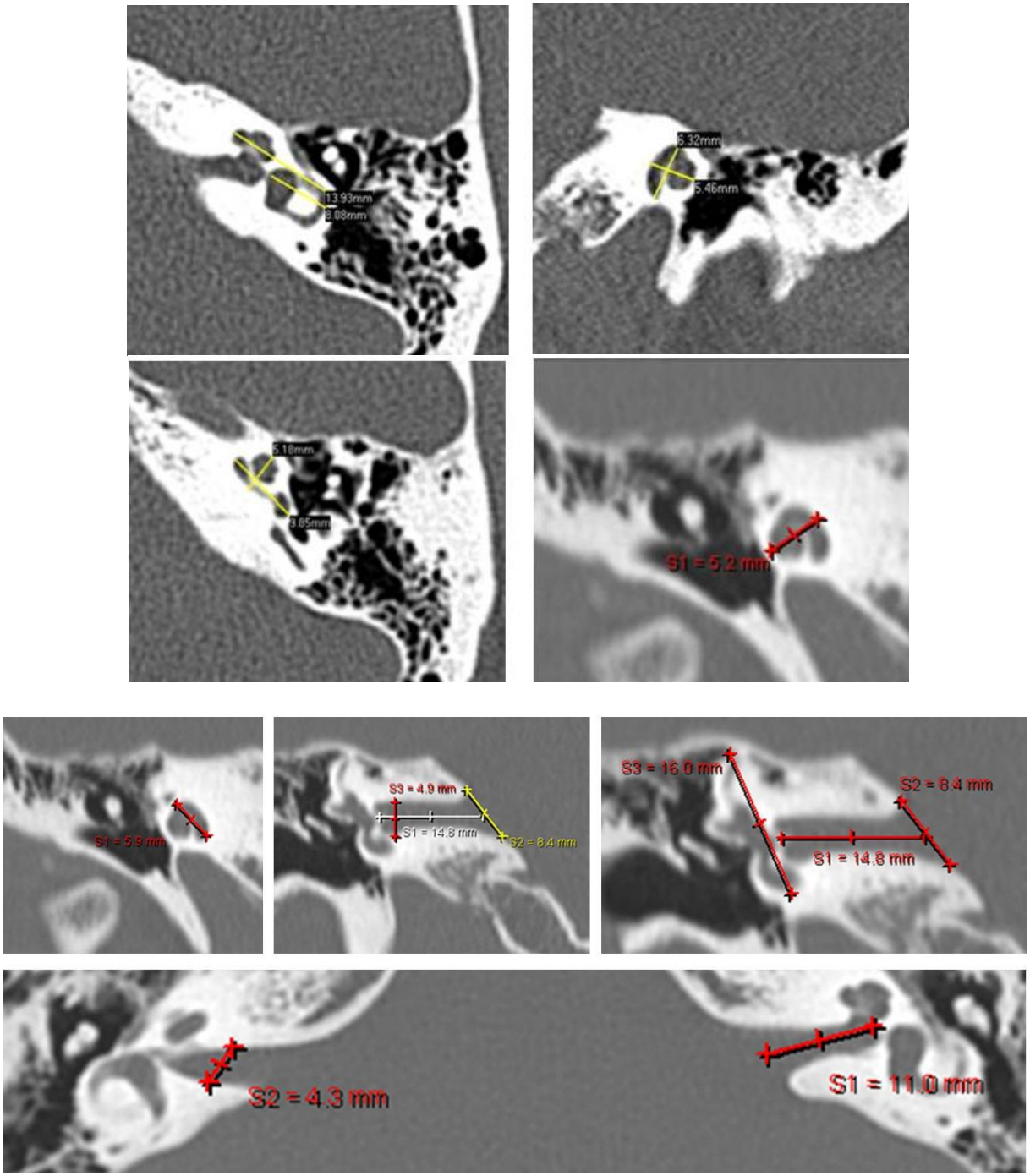


Fig. 2 - MRI and CT scans showing normal inner ear anatomy. The total length of the cochlear partition ranges from 38.6 to 45.6 mm (average 42.0 mm.). The length of the basal turn (53% of the total length) ranges from 20.3 to 24.3 mm. The width of the internal auditory canal is between 4.85 and 5.02 mm. The height ranges from 4.39 to 4.62 mm and the length from 11.22 to 11.44 mm [48].

The best review of these developmental anomalies is given by Sennaroglu and Saatci [24-25], which is an update on the valuable original work by Jackler et al. [31], and the present study is essentially based on their classification (Tab. I) [45]. Table II shows the recurrence rate of different temporal bone malformations [46]. No cases of variations in the dimension of the facial recess have been reported.

COCHLEAR MALFORMATIONS	*DESCRIPTION*	*%*
Michel deformity	**Complete aplasia of all of the inner ear structures. This condition can be associated with aplasia of the internal auditory canal.**	**6**
Cochlear aplasia	**Absent cochlea in the presence of a normal, dilated, or hypoplastic vestibule and semicircular canal system. The internal meatus might be normal.**	**5**
Common cavity	**Round or ovoid structure that represents the cochlea and vestibule. The cochlear nerve might be absent.**	**8**
Cochleovestibular hypoplasia	**Cochlear and vestibular structures are clearly seen to be separate from each other. The cochlea is smaller than normal but might have a normal internal architecture (cochlea height < 4.4 mm and less than 2.5 turns). The cochlear aperture could be aplastic, and the cochlear nerve might be absent.**	**12**
Incomplete partition type I (IP1): cystic cochleovestibular malformation	**Cystic cochlea (the absence of partitions and cochlea has cystic aspects; furthermore, the modiolus and cribriform areas are absent) and dilated vestibule. Most cases have an abnormal internal auditory canal (IAC) with an absent lateral wall of the IAC.**	**20**
Incomplete partition type II (IP2): Mondini malformation	**Cystic cochlear apex (the cochlea has a normal basal turn but the medial and apical turns are fused together, leading to a one and and a half turn cochlea)** **Minimally dilated vestibule** **Large vestibular aqueduct**	**19**
Incomplete partition type III (IP3); X-linked deformity/deafness.	**This condition is similar to IP1, except for the presence of the interscalar septa; the modiolus is absent. It could be misdiagnosed as a mixed type hearing loss.**	**2**

Tab. I. – Classification of cochlea malformations [45].

Enlarged vestibular aqueduct (EVA) is the most common radiologically detectable inner ear malformation that is associated with hearing loss. Approximately 80% of hearing impaired patients with at least one mutation in the *SLC26A4* gene presented EVA at neuroimaging. Nevertheless, EVA can be associated with other conditions, such as Waardenburg syndrome or BOR (branchio-oto-renal) syndrome.

MALFORMATIONS	*FREQUENCY*
Malformed ossicles	67%
Abnormal oval window	57%
Facial Nerve Anomalies	57%
Enlarged Vestibular Aqueduct (EVA)	52%
Enlarged Cochlear Aqueduct (ECA)	43%
Abnormal round window	29%
Middle ear aplasia	19%

Tab. II – Recurrence rates of the temporal bone malformations [46].

Malformations of the inner ear that represent an absolute contraindication to the IC are the bilateral aplasia of the cochlea or cochlear nerve. Aplasia of the cochlear nerve is frequently in the presence of a common cavity, CHARGE association and when the internal auditory canal has a diameter of less than 2 mm [25,47]. Other causes are rare syndromes such as LAMM [49] and Möbius. Hypoplasia of the cochlear nerve is not an absolute contraindication to the CI, but it could lead to reduced performances [12,13].

Anomalies of the facial nerve, malformations that increase the risk of gusher (such as enlarged vestibular aqueduct, absence or hypoplasia of the modiolus, dilation of the vestibule or semicircular canals and stenosis of the round window), common cavities, and abnormal vessel paths can complicate the surgical approach.

Finally, some malformations of the inner ear, such as common cavity, absence or hypoplasia of the modiolus, can complicate the fitting and can require repeated control mapping due to the instability of the electrode array inside the malformed cavity.

In summary, the various types of inner ear malformations could have quite different prognoses for auditory performance after a CI depending on the degree of the dysplasia. It should be emphasised that no single centre has, as yet, assembled a very large series of cochlear implants in dysplastic ears or brain abnormalities; thus, a clear picture of the expected outcomes in different groups is not possible at this stage.

1.2 Brain anomalies and hearing loss

A comprehensive review of brain anomalies is not an objective of the present study. Even if updating revisions of central nervous system (CNS) abnormalities are available in the literature, they were not discussed in this research. In theory, every CNS lesion can be responsible for hearing loss. In clinical practice, CNS lesions are usually represented by: neoplasms/neoformations, malformations, vascular/ischemic and gliotic lesions, white-matter disorders, demyelinating disorders, and viral/bacterial infections (meningitis and cytomegalovirus infections).

1.3 Objectives

The aims of this work were to study the diagnostic value of HRCT and MRI in children who have sensorineural hearing loss and who were candidates for cochlear implants; we also aim to analyse anatomic abnormalities of the ear and brain in patients who underwent CI. We analysed the effects of ear malformations and brain anomalies on the CI outcomes. Finally, we described the genetic mutations that we found in the study group. A control study group of implanted patients without ear and brain anomalies was obtained (virtually) from clinical data and literature data for statistical purposes.

MATERIALS AND METHODS

This study is a retrospective observational review of cochlear implant outcomes among hearing-impaired children who presented ear and/or brain anomalies at neuroimaging investigations with MRI and HRCT. Furthermore, genetic results from molecular genetic investigations (*GJB2*/*GJB6* and, additionally, in selected cases, *SLC26A4* or *mitochondrial-DNA* mutations*)* on this study group were herein described. Longitudinal and cross-sectional analyses were conducted using statistical tests. To create more homogenic groups and more study-specific findings (e.g., EVA) and to obtain more significant analysis, the main study group was divided into different subgroups, which were named with alphabetic letters, as follows (Tab. III):

STUDY GROUPS	INCLUSION CRITERIA
MAIN STUDY GROUP	Cochlear implant recipients who had less than 18 years of age at the time of surgery and who presented neuroradiological findings at pre-operative neuroimaging investigations.
SUBGROUP A	Patients with inner ear malformations (with or without brain anomalies)
SUBGROUP B	Patients with internal auditory canal stenosis
SUBGROUP C	Patients with only inner ear malformations (without brain anomalies)
SUBGROUP D	Patients with only brain anomalies (without inner ear malformations)
SUBGROUP E	Patients with inner ear malformations AND brain lesions or abnormalities (with brain anomalies)
SUBGROUP F	Monolateral CI
SUBGROUP G	Bilateral CI
SUBGROUP H	< 3 years of age at the time of surgery
SUBGROUP I	> 3 years of age at the time of surgery
SUBGROUP J	Patients with genetic mutations
SUBGROUP K	Cytomegalovirus
SUBGROUP L	Meningitis (as a cause of hearing loss)
SUBGROUP M	Patients who presented EVA
SUBGROUP N	CHARGE association
SUBGROUP O	Demyelination
SUBGROUP P	Gliosis
SUBGROUP Q	Leukomalacia
SUBGROUP R	Only cochlear malformations

Tab III – The study groups of the present research.

A control study group was created starting from literature data and randomised selected cases (from our casuistry) of implanted children without neuroradiological findings. A long-term follow-up was performed, which reported that the Geers and Moore score was achieved at 3, 6, 12, 24, and 36 months. Each of the subgroups was compared with the control study group. Furthermore, the subgroups were compared with each other only if the same patients were not present in either. Specific findings were reported as singular cases. A non-parametric test was used for statistical analysis: the Mann-Whitney U test. Furthermore, we used the ANOVA test (analysis of variance) for the comparison between patients with monolateral CI and patients with bilateral CI.

2.1. Audiological assessment.

Before implantation, all of the children had documented severe to profound or profound sensorineural HL (hearing loss) and failed an appropriate hearing-aid trial. Each patient has been investigated from an audiological point of view using objective tests, such as OAEs (otoacoustic emissions), ABR (auditory brainstem response), and ASSR (auditory steady state response), to estimate the pure-tone threshold and, in selected cases, to perform ECochG (electrocochleography). When possible, the audiological assessment was completed using behavioural and tonal audiometry with and without previously described hearing aids. Children of 6-36 months of age underwent conditioned orientation reflex (COR) and visual reinforcement audiometry (VRA) tests to investigate the tonal threshold at low frequencies and to assess the effectiveness of the hearing aids. From the age of three to four years, the pure-tone hearing thresholds can be obtained by motivational games that range from peep shows to finger-raising techniques, and at an age of six years, most children can perform formal audiometry the same as that used in adults. The testing is dependent only on the degree of cooperation of the child and the experience of the tester. Micro-otoscopy,

tympanometry and recording of stapedius reflex thresholds were part of the test procedure. The interpretation and diagnostic validity of stapedius-reflex-threshold testing in children are similar to the testing of adults, but the test might be difficult to perform in very young children.

2.2. Imaging data

High resolution HRCT (High Resolution Computed Tomography) and MRI (Magnetic Resonance Imaging) were conducted in all patients to obtain a radiological examination of the temporal bone and brain. If necessary, children underwent neuroradiological scans during general anaesthesia. HRCT scanning with contiguous 0.3 - 1 mm thick images through the petrous temporal bone in the axial and direct coronal planes was performed. Ear, brainstem and encephalon MRI scanning was acquired at 1.5 T and included high resolution axial and coronal T2-weighted imaging axial and coronal T1-weighted imaging, using CISS (Constructive Interference in Steady State) and FIESTA (Fast Imaging Employing Steady-state Acquisition). If contrast was required, then post-contrast T1-weighted images were acquired in all three planes. CISS and FIESTA are a gradient-echo MRI sequence that are used to investigate a wide range of pathologies when routine MRI sequences do not provide the desired anatomic information. MRI brain scanning was also acquired at 1.5 T and included axial T2-weighted imaging, axial fast fluid-inversion recovery sequence (FLAIR) imaging, axial T1-weighted inversion recovery imaging and, if contrast was required, axial T1-weighted imaging.

The neuroimaging findings of the temporal bone were categorised as:

1) Cochlear malformations
2) Vestibular and semicircular canal malformations
3) IAC (internal auditory canal) anomalies
4) EVA (enlarged vestibular aqueduct)

The vestibular aqueduct is defined as enlarged if its diameter is greater than 1.5 mm at the midpoint. Vestibular and labyrinthine abnormalities included partial SCC aplasia and total SCC aplasia. Cochlear malformations were subsequently divided as follows:

1) Cochlear malformations
    a. Common cavity deformity.
    b. Cochlear hypoplasia.
    c. Incomplete partition type I (IP-I).
    d. Incomplete partition type II (IP-II) (Mondini deformity).
    e. Incomplete partition type III (IP-III)
    f. Basal turn dysplasia.

Mondini malformation is a cochlear anomaly that is characterised by a fusion of the apical and middle turn (only one and a half turns is present out of the normal two and a half turns). The brain MRI scans of all of the patients were reviewed, and all of the abnormal findings were identified and classified as follows:

1) Malformations
    a. Aplasia, dysplasia or hypoplasia
    b. Dilatations
    c. Arnold-Chiari malformations
2) Neoformations
    a. Neoplasms (benign or malignant)
    b. Cystic lesions
3) White matter disorders
    a. Leukomalacia
    b. Leukodystrophy
    c. Demyelination

4) Gliotic lesions (including cytomegalovirus infections and ischemic lesions)
5) Other abnormalities

2.3. Genetic and molecular analysis

Informed consent was obtained from patients and parents according to current national rules and laws. Molecular genetic studies of the *GJB2, GJB6, SLC26A4* genes and mitochondrial DNA (mit-DNA) were performed in 77 patients. Genomic DNA was extracted by standard protocols from peripheral blood leukocytes of patients. Direct DNA sequencing of the *GJB2* gene (including analysis of the entire coding region) was performed. PCR amplification of the coding 21 exons, the flanking and promoter regions of the *SLC26A4* gene was performed using specific primers. Amplification reactions were performed in a final volume of 25 ml containing 100 ng of genomic DNA, 200 mmol/l dNTPs, 10 mmol/l each primer 1.5 mmol/l $MgCl_2$, and 1 U of Taq polymerase. After 5 min of denaturation at 94°C, 35 PCR cycles were carried out, each cycle comprising 45s of denaturation at 94 °C, 45s of annealing at 60 °C and 80s of extension at 72°C. Direct sequencing of the PCR products on both strands was performed on an ABI PRISM 3130xl sequencer, using the ABI BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems by Life Technologies).

2.4. Speech perception (pre-operative assessment and post-operative outcomes):

Behavioural measures of speech perception scores [50-54] are routinely completed in all children in our study at follow-up visits and a database of these outcomes is maintained. The database also includes patient demographics (age at implant, gender, duration of implant use), audiological characteristics (congenital vs. progressive loss) and relevant medical history (other medical conditions, such as craniofacial syndromes).

Perceptive abilities are usually classified into 4 types of increasing complexity performances [52]:

1) Detection: ability to respond to the presence or absence of a signal;
2) Discrimination: ability to distinguish differences or similarities between two stimuli;
3) Identification: ability to choose an item from a known set;
4) Recognition: ability to repeat or imitate spoken stimuli.

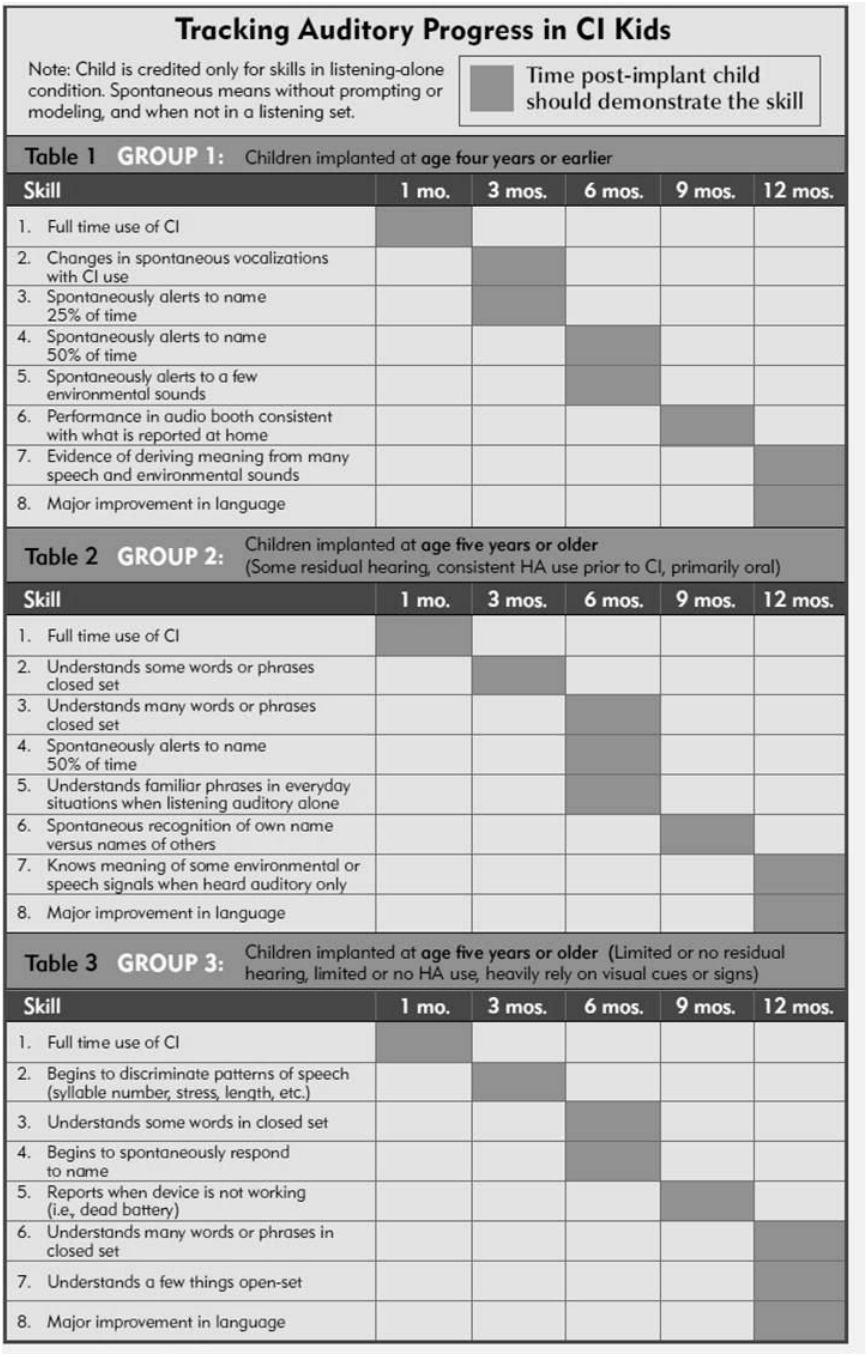
The achieved performance enabled us to include each patient in a specific perceptual category. Geers and Moog propound perceptive classification with six categories, which are based on performances that have been analysed with sets of specific tests (Tab. IV) [14]:

Category 0	no detection of verbal sounds
Category 1	detection of verbal sounds
Category 2	discrimination of verbal sounds
Category 3	identification of verbal sounds
Category 4	closed set vowel recognition
Category 5	closed set consonant recognition
Category 6	open set recognition

Tab IV- Geers and Moog perceptive categories classification.

Geers & Moog perception was used for the present study. A comparison of specific speech perception tests was conducted between hearing impaired children with normal anatomy (called "well babies") and those who were affected by cochleovestibular and brain abnormalities. An excellent tool for monitoring progress in young children is the Clinical Red Flag Procedure [50], which is a matrix of auditory benchmarks that has been established for identifying children who are progressing at a slower-than-expected rate. These benchmarks are based on research and clinical findings that document the listening skills that are achieved by the average CI child during the first year of device use (fig. 3). Three

different groups of CI children reflect different pre-implant characteristics and show different patterns of skill achievement [50].



Tracking Auditory Progress in CI Kids

Note: Child is credited only for skills in listening-alone condition. Spontaneous means without prompting or modeling, and when not in a listening set.

Time post-implant child should demonstrate the skill

Table 1 GROUP 1: Children implanted at **age four years or earlier**

Skill	1 mo.	3 mos.	6 mos.	9 mos.	12 mos.
1. Full time use of CI	■				
2. Changes in spontaneous vocalizations with CI use		■			
3. Spontaneously alerts to name 25% of time		■			
4. Spontaneously alerts to name 50% of time			■		
5. Spontaneously alerts to a few environmental sounds			■		
6. Performance in audio booth consistent with what is reported at home				■	
7. Evidence of deriving meaning from many speech and environmental sounds					■
8. Major improvement in language					■

Table 2 GROUP 2: Children implanted at **age five years or older** (Some residual hearing, consistent HA use prior to CI, primarily oral)

Skill	1 mo.	3 mos.	6 mos.	9 mos.	12 mos.
1. Full time use of CI	■				
2. Understands some words or phrases closed set		■			
3. Understands many words or phrases closed set			■		
4. Spontaneously alerts to name 50% of time			■		
5. Understands familiar phrases in everyday situations when listening auditory alone			■		
6. Spontaneous recognition of own name versus names of others				■	
7. Knows meaning of some environmental or speech signals when heard auditory only					■
8. Major improvement in language					■

Table 3 GROUP 3: Children implanted at **age five years or older** (Limited or no residual hearing, limited or no HA use, heavily rely on visual cues or signs)

Skill	1 mo.	3 mos.	6 mos.	9 mos.	12 mos.
1. Full time use of CI	■				
2. Begins to discriminate patterns of speech (syllable number, stress, length, etc.)		■			
3. Understands some words in closed set			■		
4. Begins to spontaneously respond to name			■		
5. Reports when device is not working (i.e., dead battery)				■	
6. Understands many words or phrases in closed set					■
7. Understands a few things open-set					■
8. Major improvement in language					■

Fig. 3 - Clinical red flags for slow progress in children with cochlear implants. Red flag Matrix for monitoring listening progress in the first year of CI use. Robbins (2005). *Note that full-time implant use is an unconditional prerequisite to auditory development. If a child is not wearing the implant during all waking hours—at home, school, and other activities, then these benchmarks are not applicable. Children who fail to bond to their device and to wear it full-time within a few weeks of initial stimulation may exhibit insufficient progress and are at high risk of becoming non-users of their implants.

It appears evident that in the "well babies", the perceptual expected results after 3 months of use of the CI essentially comprise the detection of voice and first discrimination abilities until the recognition of words and phrases without the help of lip reading at 1 year of CI use. In summary, the expected perceptual results were the achievement of perceptual category 2 at 3 months from the CI activation, perceptual category 4 at 6 months and perceptual category 6 at 12 months. The follow-up initially should be very tightly controlled and should be performed in the first year after surgery, at 3, 6, 9 and 12 months and then yearly. The evaluation of perceptual skills and communication has been made by the administration of different tests according to the stage of language development of the child (pre-verbal stage, transitional stage and functional stage).

2.4.1. Listening Progress Profile (Lip) (developed by Archbold 1994)

The LIP is a profile that is designed to monitor changes in early auditory perception of young children and is most commonly used with children who use cochlear implants. Two types of nonlinguistic sound perception abilities are monitored using this profile: environmental sound awareness and environmental sound discrimination. LIP also monitors speech perception abilities [51]. The LIP identifies three different skills: response, discrimination, and identification. The response skill is used to describe the detection of a sound. Discrimination is used to describe the ability for the child to choose correctly between two different sounds. Identification is used to describe the ability to correctly choose the target sound from an open set of sounds. The child is then scored on each of these skills in the following way: N (Never/not known), S (Sometimes), and A (Always). These responses can be elicited or observed. The profile is structured as a list of behaviours or skills such as “Response to Environmental Sounds”.

There are six skills that pertain to nonlinguistic sounds and ten skills that relate to linguistic sounds:

1. Response to a drum
2. Response to a musical instrument
3. Discrimination between 2 different instruments
4. Discrimination between a loud and quiet drum
5. Discrimination between a single and repeated drum
6. Identification of environmental sounds
7. Speech detection (elicited)
8. Speech detection (spontaneous)
9. Linguistic sound detection
10. Short/Long discrimination of verbal material
11. Single/Repeated discrimination of verbal material
12. Soft/Loud discrimination (intensity discrimination)
13. Discrimination of at least 2 linguistic sounds
14. Discrimination of at least 5 linguistic sounds
15. Discrimination between 2 words of different lengths
16. Identification of own name

Additionally, little information is offered on the types of sounds that the child can identify or comprehend. Using the LiP test, we can see that the median percentage is achieved by the single age groups at different testing times after implantation. Children who are older than 5 years at the time of their implantation reached the maximum score on the LiP 1 year after implantation. Children between 3 and 5 years at the time of their implantation scored highest 1.5 years after implantation. The children who received implants at the youngest ages (<3 years) reached their highest possible value approximately 2 years after implantation.

Age group (y) at time of implantation	LiP pre (%)	LiP ff* (%)	LiP 1 month (%)	LiP 3 months (%)	LiP 6 months (%)
Chance score	n.a.	n.a.	n.a.	n.a.	n.a.
0 – 1	1.2	6.0	8.3	21.4	40.5
1 – 2	2.4	7.1	23.8	42.9	59.5
2 – 3	4.8	11.9	35.7	50.0	66.7
3 – 4	9.5	38.1	47.6	64.3	82.1
4 – 5	14.3	38.1	61.9	83.3	90.5
5 – 6	29.8	45.2	70.2	85.7	92.9
6 – 7	31.0	71.4	86.9	88.1	96.4
>7	51.2	69.0	85.7	95.2	97.6

* ff = first fitting

Age group (y) at time of implantation	LiP 1 year (%)	LiP 1.5 years (%)	LiP 2 years (%)	LiP 3 years (%)	LiP 4 years (%)	LiP 5 years (%)
Chance score	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
0 – 1	57.14	65.5	100	-	-	-
1 – 2	69.05	94.0	97.6	100	100	100
2 – 3	88.10	97.6	100	100	100	100
3 – 4	95.24	100	100	100	100	100
4 – 5	97.62	100	100	100	100	100
5 – 6	100	100	100	100	100	100
6 – 7	100	100	100	100	100	100
> 7	100	100	100	100	100	100

Fig. 4. Evaluation of Auditory Responses to Speech - Normative Data Med-El, Innsbruck (1998)

2.4.2. Early Speech Perception Test (ESP) (Moog & Geers, 1990)

Italian version: PCAP (Test di misurazione delle Prime Categorie Percettive) (Arslan et al. 1997). This test measures the child's ability to discriminate different words based on specific perceptual features. Therefore, it is possible to include each child in one of four perceptual categories [14]. The standard version was designed to obtain accurate information about the progression of speech discrimination skills in children who have profound hearing impairments as they develop. The standard verbal version was designed for children who are at least 6 years. The stimuli are composed of 36 words that are presented in an auditory-only condition as three subtests of 12. The format is closed-set. Each subtest is administered using both visual and auditory input to differentiate speech perception skills from language ability. The low verbal version was designed to estimate speech perception abilities in very young children (a minimum of 2 years) who have limited verbal abilities. Stimuli comprise words

that vary in pattern as well as spondees and monosyllabic words presented in sets of four. The format is a four-item closed-set format and can be presented via live voice or a recording. Test materials constitute objects (toys) instead of pictures.

2.4.3. GASP (Glendonald Auditory Screening Procedure) (Erber, 1982)

Italian version: TAP (Test delle Abilità Percettive) (Arslan et al. 1997). This test measures the ability to understand simple sentences, and it also uses only one type of sentence structure (questions). This arrangement is useful because children can become confused when faced with different sentence structures (questions, commands or statements) in the same test. Children are allowed to either repeat the question or to answer it. This test comprises 3 subtests [52]: 1) detection, 2) identification and 3) comprehension.

1) DETECTION:

a. purpose
    i. to determine the device settings and to check whether the CI is working;
    ii. to attract a child's attention and to orient him or her to the listening task;
    iii. to determine which sounds are available to the child;
b. response
    i. repeatedly says a new word in a meaningful context.

There is rarely any need to spend much time at this level, although it could be worthwhile to help the child to detect those sounds, such as fricative consonants, which are low in acoustic energy.

2) IDENTIFICATION:

a. purpose
    i. to apply labels to speech stimuli that can be discriminated;

ii. to learn speech patterns;

b. response

i. point to an item named by the speaker, repeat stimulus, write stimulus.

When writing sentences, it is a good idea to construct sentences that have some relevance to the children. It is best to attempt to make sentences that are sufficiently different in length and/or pattern to enable all children in the group to achieve some success in identification.

When presenting an identification task, include "no sound" (the absence of sound) as a response option. This option helps the child to become aware of the possibility that he or she might hear nothing, and thus, the child can learn to indicate that the IC is off, has a dead battery, or is faulty. A response of "no sound" could also indicate that the talker is too far away from the child.

3) COMPREHENSION:

a. purpose

i. To understand the meaning of a spoken stimulus

ii. To make complex associations between sounds and events/objects or between the sounds themselves

b. response

i. The child performs the required task or answers questions.

2.4.4. Northwestern University – Children's Perception of Speech (NU-CHIPS) - (Elliot and Katz, 1980)

Italian version: T.I.P.I.1 (Test di Identificazione Parole Infantili 1) (Arslan et al.1997). NU-CHIPS is a closed-set picture-pointing word recognition test for children. This test is composed of 50 words that are familiar to three-year-old children in four randomisations called forms. The test includes one CD-Rom, which contains two picture books with 50

monochrome plates, with four pictures per plate. There are two recordings, with one male speaker and one female speaker. [53]

2.4.5. Word Intelligibility by Picture Identification (WIPI) (Ross and Lerman, 1979)

Italian version: T.I.P.I.2 (Test di Identificazione Parole Infantili 2) (Arslan et al. 1997). This test is a closed-set discrimination task in which the child must identify the stimulus word from a set of six pictures. The recommended age is a minimum of 4 years. The stimuli are composed of four lists of 25 single-syllable words. Chance performance amounts to a score of approximately 18%. This discrimination task is more difficult than the majority of other closed-set discrimination tasks in that the vocabulary level is higher and the response choices differ in fine segmental information [54].

3. RESULTS

Between 1st January 1996 and 1st April 2012 at the ENT-Audiology Department of the University Hospital of Ferrara, 620 cochlear implantations were performed. There were 426 implanted children at the time of the present study (who were <18 years).

Reviewing the neuroradiological findings of the 426 implanted children revealed no abnormalities in 283 cases and ear and / or brain anomalies in 143 cases (33.6% of 426). Among these 143 patients (64 females and 79 males), 123 children had unilateral cochlear implantation (68 in the right ear; 55 in the left ear), and 20 underwent bilateral cochlear implantations (3 simultaneously, 17 sequentially). The age of the main study group (143 implanted children) ranged from 9 months and 16 years (mean = 4.4; median = 3.0). These patients showed an average period of cochlear implant use of 74 months.

The CT and MRI scans of 143 children included in the present study were re-evaluated, and the following abnormalities were detected: in 69 cases (48.2% of 143), ear malformations were present, of which 55 had bilateral ear involvement; therefore the implanted ear was necessarily the malformed ear; in 11 children, the malformed ear was the right ear (of which only in one case the malformed side was the implanted side), and in 3 cases, the malformation was detected in the left side (also in this series only one child underwent cochlear implantation in the malformed ear); 74 cases (51.7% of 143) presented only brain anomalies. A total of 45 patients (31.5% of 143) presented either ear or brain abnormalities. Table V shows different aetiologies of hearing loss that we found in our series. Details of the identified cochleovestibular (inner ear) malformations are presented in Table VII and VIII.

Aetiology	Number of Patients	%
Unknown	27	18.9
Cytomegalovirus infection	26	18.2
GJB2 mutations	24	16.8
Acquired conditions (prematurity, perinatal suffering/icterus)	16	11.2
Enlarged Vestibular Aqueduct (EVA)	14 (4 Pendred Syndromes)	9.8
Cochleovestibular malformations	14	9.8
Meningitis/encephalitis	12/1	9.1
CHARGE association	3	2.1
Hydrocephalus	2	1.4
Waardenburg Syndrome (with dilated vestibule and bilateral cochlear dysplasia)	1	0.7
Möbius Syndrome (with microtia and facial nerve aplasia)	1	0.7
Williams Syndrome (with EVA and semicircular canal dysplasia)	1	0.7
Other conditions (neurosurgery)	1	0.7
Total	**143**	**100**

TAB V - Suspected main aetiology of hearing loss among 143 children who underwent cochlear implantation and presented ear or brain anomalies.

Demographic groups and audiological features are resumed in Table VI.

	EXTERNAL EAR MALFORMATIONS (TOTAL N°= 3 CASES)	MIDDLE EAR MALFORMATIONS (TOTAL N°= 18 CASES)	INNER EAR MALFORMATIONS (TOTAL N°= 30 CASES)	BRAIN ANOMALIES (TOTAL N°= 119 CASES)	WITHOUT BRAIN ANOMALIES (TOTAL N°= 24 CASES)
SEX (FEMALE:MALE)	**1:2**	**9:9**	**11:19**	**55:64**	**9:15**
MEAN AGE (in years) AT THE TIME OF SURGERY	**3.0**	**3.0**	**4.4**	**4.0**	**7.0**
MEAN PERIOD (in months) OF USING COCHLEAR IMPLANT	**78**	**73**	**74**	**75**	**71**
IMPLANTED EAR (°)	**2L, 1R**	**8L, 7R, 3B**	**11L, 15R, 4B**	**42L, 61R, 16B**	**13L, 7R, 4B**
% OF PROGRESSIVE HEARING LOSS	**-**	**22.2%**	**30.0%**	**45.3%**	**54.1%**
CYTOMEGALOVIRUS INFECTIONS	**-**	**3**	**2**	**26**	**-**
MENINGITIS	**-**	**-**	**1**	**11**	**1**
GENETIC MUTATIONS	**-**	**2**	**5**	**21**	**3**
SYNDROMES	**3**	**3**	**5**	**6**	**4**
UKNOWN AETIOLOGY	**-**	**3**	**-**	**26**	**1**
OTHER CONDITIONS (*)	**-**	**2**	**2**	**19**	**1**

Tab. VI – Demographic, clinical and audiological data and aetiologies of hearing loss; ° (R=RIGHT; L=LEFT; B=BILATERAL); * (infant cerebral palsy, prematurity, perinatal suffering, hydrocephalus, ischemia, neonatal icterus).

	COCHLEAR MALFORMATIONS (TOTAL N°=21 CASES)	VESTIBULAR AND SEMICIRCULAR CANAL MALFORMATIONS (§) (TOTAL N°=24 CASES)	ABNORMAL INTERNAL AUDITORY CANAL (•) (TOTAL N°=15 CASES)	EVA (N°=21 CASES)
SEX (FEMALE:MALE)	6:15	10:14	10:5	10:11
MEAN AGE (in years) AT THE TIME OF SURGERY	4	4	5	7
MEAN PERIOD (in months) OF USING COCHLEAR IMPLANT	75	77	84	54
IMPLANTED EAR (°)	8L, 11R, 2B	6L, 13R, 5B	7L, 8R	12L, 7R, 2B
MALFORMED SIDE (°)	1L, 2R, 18B	1L, 2R, 21B	1R, 14B	1L, 3R, 17B
% OF PROGRESSIVE HEARING LOSS	28.6%	41.6%	26.6%	71.4%

Tab. VII – Anatomic distribution of inner ear malformations; ° (R=RIGHT; L=LEFT; B=BILATERAL); §(6 HYPOPLASIAS; 7 DILATATIONS; 3 APLASIAS); •(7 STENOSIS; 8 DILATATIONS).

	COMMON CAVITY	COCHLEAR HYPOPLASIA (TOTAL N°= 6 CASES)	INCOMPLETE PARTITION TYPE 1 (TOTAL N°= 2 CASES)	INCOMPLETE PARTITION TYPE 2 (TOTAL N°= 7 CASES)	INCOMPLETE PARTITION TYPE 3 (TOTAL N°=2 CASES)	COCHLEAR BASAL TURN DYSPLASIA (TOTAL N°= 4 CASES)
SEX (FEMALE:MALE)	-	2:4	0:2	3:4	1:1	0:4
MEAN AGE (in years) AT THE TIME OF SURGERY	-	5	3	5	7	2
MEAN PERIOD (in months) OF USING COCHLEAR IMPLANT	-	59	82	85	77	73
IMPLANTED EAR (°)	-	2L, 4R	1L, 1R	2L, 4R, 1B	1L, 1R	2L, 1R, 2B
MALFORMED SIDE (°)	-	1L, 1R, 4B	2B	1R, 6B	2B	4B
% OF PROGRESSIVE HEARING LOSS	-	40%	-	28.6%	50%	25%

Tab. VIII – Types of cochlear malformations; ° (R=RIGHT; L=LEFT; B=BILATERAL).

Finally, Table IX reports in detail the brain anomalies that were found, with the total number of cases for each type.

Type of lesion/malformation	Total number of cases among 143 implanted children
Gliosis	32
Dismyelination/demyelination	25
Leukomalacia	24
Pineal cyst	9
Arnold-Chiari malformation (type 1)	7
Cerebellar hypoplasia	6
Cortical dysplasia	5
Calcifications	3
Arachnoid cyst	3
(External) Hydrocephalus	3
Dilated lateral ventricles	2
Corpus callosum hypoplasia	2
Dilated fourth ventricle	2
Trigonocephaly	2
Facial nerve aplasia	1
Pinealoma	1
Hamartoma	1
Hydrocephalus	1
Bulbar atrophy	1
Cisternal dilatation	1
Malignant neoplasm of encephalon (after surgery)	1
Pellucid septum cyst	1
Dilated subarachnoid space	1
Focal ischemic lesions	1
Microcephaly	1
Lipoma	1
(Occipital) Myelomeningocele	1
Leukodystrophy	1
Pachygyria	1
Temporal lobe hypoplasia	1

TAB IX – Brain anomalies that were found among 143 implanted children.

For statistical purposes, the main group was divided into subgroups, as follows (table X):

GROUPS	INCLUSION CRITERIA	NUMBER OF CASES
MAIN STUDY GROUP	Cochlear implant recipients who were less than 18 years of age at the time of surgery and who presented neuroradiological findings at pre-operative neuroimaging investigations.	**143**
SUBGROUP A	Patients with inner ear malformations (with or without brain anomalies)	**23**
SUBGROUP B	Patients with internal auditory canal stenosis	**7**
SUBGROUP C	Patients with only inner ear malformations (without brain anomalies)	**13**
SUBGROUP D	Patients with only brain anomalies (without inner ear malformations)	**102**
SUBGROUP E	Patients with inner ear malformations AND brain lesions or abnormalities (with brain anomalies)	**17**
SUBGROUP F	Monolateral CI	**123**
SUBGROUP G	Bilateral CI	**20**
SUBGROUP H	< 3 years of age at the time of surgery	**61**
SUBGROUP I	> 3 years of age at the time of surgery	**82**
SUBGROUP J	Patients with genetic mutations	**35**
SUBGROUP K	Cytomegalovirus	**26**
SUBGROUP L	Meningitis (as the cause of the hearing loss)	**13**
SUBGROUP M	Patients who presented EVA	**21**
SUBGROUP N	CHARGE association	**3**
SUBGROUP O	Demyelination	**25**
SUBGROUP P	Gliosis	**36**
SUBGROUP Q	Leukomalacia	**25**
SUBGROUP R	Patient with only cochlear malformations	**9**

Table X – Different subgroups were defined to implement the statistical analysis.

Controls	N	Mean	StDev	Percentiles (25°	50°	75°)
3 m	133	2,113	1,579	1,00	2,00	3,00
6 m	127	2,945	1,844	1,00	3,00	4,00
1 y	117	4,120	1,890	2,00	5,00	6,00
2 y	100	4,940	1,693	4,00	6,00	6,00
3 y	70	5,243	1,408	4,75	6,00	6,00
4 y	44	5,432	1,301	6,00	6,00	6,00
5 y	29	5,896	0,409	6,00	6,00	6,00
6 y	24	6,000	0,000	6,00	6,00	6,00

Fig. 5. – Perceptual outcomes of the MAIN STUDY GROUP with a cochlear implant at the six-year follow-up.

After 3 months of using the cochlear implant, more than half of the patients in the main study group did not achieve the 3th category of perception at the Geers & Moog scale; in the same group, the 50% of the children did not reach the 4th category at the 6-month follow-up, nevertheless they achieved the 5th category 6 months after (1-year follow-up). Only 2 years after cochlear implant activation, the majority of the patients attain a 6th perceptual category at the Geers & Moog scale (fig. 5).

Statistical results are reported in full as the following graphs (fig. 5-15). These graphs show the comparison between the control group and each of the subgroups; nonetheless, different subgroups were compared.

Graphs are structured as follows: on the abscissa axis are reported the number of cases, and they are distributed over the time of the 3, 6, 12, 24 and 36 month follow-ups, using a colour code for identification (red for the 3-month control, green for the 6-month control, blue for the 12-month control, violet for the 24-month control and azure for the 36-month control).

There was a statistically significant difference ($p \leq 0.01$) between the control group and the subgroup B (patients with internal auditory canal stenosis) at the 6-months follow-up. Similar results were obtained comparing control group and subgroup Q (patients affected by leukomalacia).

At the 1-year and long-term (2-3 years) follow-ups, statistically significant differences ($p \leq 0.05$) were also found comparing control group and subgroups A,B, D and E, respectively.

Comparing subgroups C and P we found that the first one achieved the "identification of verbal sounds" 6 months after device activation and the “vowel recognition” in closed set tests 6 months later; while the subgroup P more slowly reached the same perceptual skills. Nevertheless, at the long-term follow-up (2 years later) the results achieved by the two groups are optimal and similar (Fig. 8).

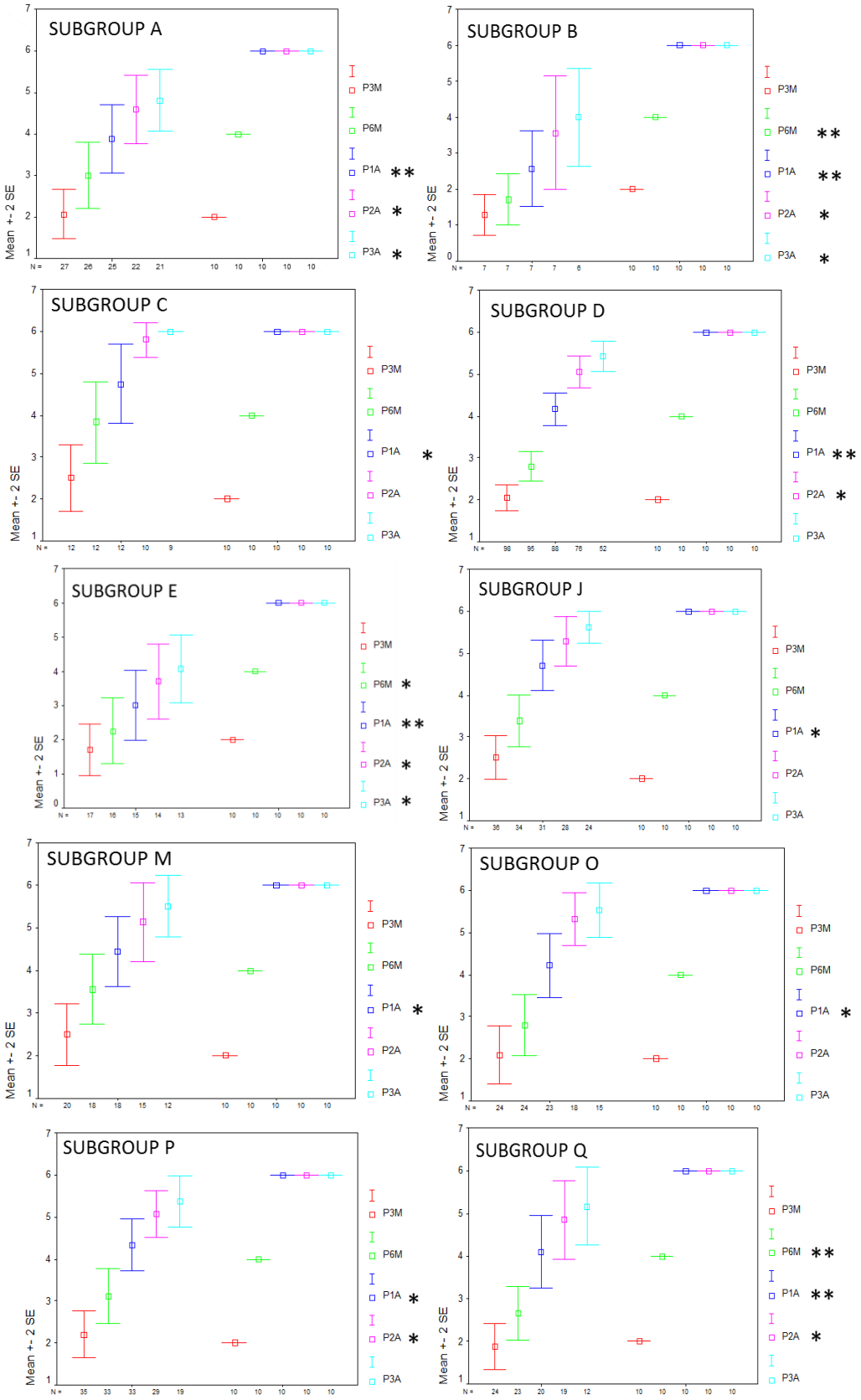


Fig 6. – In the figure are reported all of the statistical graphs that were obtained from the comparison between the subgroups A, B, C, D, E, J, M, O, P, and Q and the control group. Colour code for identification (red for the 3-month control, green for the 6-month control, blue for the 12-month control, violet for the 24-month control and azure for the 36-month control). * $P \leq 0.05$; ** $P \leq 0.01$.

SUBGROUP A

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	27	26	25	22	21	11	7	3	2
Mean	2,0741	3,0000	3,8800	4,5909	4,8095	4,7273	5,7143	6,0000	6,0000
Std. Deviation	1,5671	2,0199	2,0478	1,9435	1,6917	1,9022	,7559	,0000	,0000
Median	2,0000	2,5000	4,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP B

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	7	7	7	7	6	4	2	1	1
Mean	1,2857	1,7143	2,5714	3,5714	4,0000	4,7500	6,0000	6,0000	6,0000
Std. Deviation	,7559	,9512	1,3973	2,0702	1,6733	1,5000	,0000	,	,
Median	1,0000	2,0000	3,0000	3,0000	3,5000	5,0000	6,0000	6,0000	6,0000

SUBGROUP C

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	12	12	12	10	9	5	4	2	2
Mean	2,5000	3,8333	4,7500	5,8000	6,0000	6,0000	6,0000	6,0000	6,0000
Std. Deviation	1,3817	1,6967	1,6583	,6325	,0000	,0000	,0000	,0000	,0000
Median	2,0000	4,0000	5,5000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP D

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	98	95	88	76	52	37	25	22	15
Mean	2,0510	2,8000	4,1705	5,0526	5,4231	5,5946	5,8000	5,8182	6,0000
Std. Deviation	1,5623	1,7357	1,8459	1,6157	1,2887	1,0919	,8165	,8528	,0000
Median	1,0000	2,0000	5,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP E

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	17	16	15	14	13	7	4	2	1
Mean	1,7059	2,2500	3,0000	3,7143	4,0769	4,0000	5,5000	6,0000	6,0000
Std. Deviation	1,5718	1,9149	1,9640	2,0542	1,8010	2,0817	1,0000	,0000	,
Median	1,0000	2,0000	3,0000	3,5000	4,0000	4,0000	6,0000	6,0000	6,0000

SUBGROUP J

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	36	34	31	28	24	17	13	11	10
Mean	2,5000	3,3824	4,7097	5,2857	5,6250	6,0000	6,0000	6,0000	6,0000
Std. Deviation	1,5766	1,8425	1,6572	1,5601	,9237	,0000	,0000	,0000	,0000
Median	2,0000	3,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP K

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	24	23	23	19	14	12	9	7	4
Mean	2,3333	3,3913	4,6957	5,4211	5,4286	5,5833	5,8889	6,0000	6,0000
Std. Deviation	1,6854	1,9941	1,6634	1,3045	1,4525	,9962	,3333	,0000	,0000
Median	2,0000	3,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP L

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	9	9	8	7	5	4	3	3	3
Mean	1,3333	1,7778	3,5000	4,2857	5,6000	6,0000	6,0000	6,0000	6,0000
Std. Deviation	1,1180	,9718	2,2678	1,8898	,8944	,0000	,0000	,0000	,0000
Median	1,0000	2,0000	3,0000	4,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP M

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	20	18	18	15	12	7	7	7	5
Mean	2,5000	3,5556	4,4444	5,1333	5,5000	6,0000	6,0000	6,0000	6,0000
Std. Deviation	1,6059	1,7564	1,7564	1,8074	1,2432	,0000	,0000	,0000	,0000
Median	2,0000	3,0000	5,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP O

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	24	24	23	18	15	9	5	3	3
Mean	2,0833	2,7917	4,2174	5,3333	5,5333	5,5556	5,6000	6,0000	6,0000
Std. Deviation	1,6918	1,7932	1,8329	1,3284	1,2459	1,3333	,8944	,0000	,0000
Median	1,5000	2,0000	4,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP P

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	35	33	33	29	19	17	12	10	7
Mean	2,2000	3,1212	4,3333	5,0690	5,3684	5,5882	5,9167	6,0000	6,0000
Std. Deviation	1,6234	1,9163	1,7619	1,4864	1,3421	,9393	,2887	,0000	,0000
Median	2,0000	3,0000	5,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP Q

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	24	23	20	19	12	8	6	5	2
Mean	1,8750	2,6522	4,1000	4,8421	5,1667	5,2500	5,3333	5,2000	6,0000
Std. Deviation	1,3290	1,4957	1,8890	2,0073	1,5859	1,4880	1,6330	1,7889	,0000
Median	2,0000	3,0000	5,0000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

SUBGROUP R

	P3M	P6M	P1A	P2A	P3A	P4A	P5A	P6A	P7A
N	8	8	8	7	7	3	3	2	2
Mean	2,7500	3,7500	4,6250	5,7143	6,0000	6,0000	6,0000	6,0000	6,0000
Std. Deviation	1,5811	1,9086	1,8468	,7559	,0000	,0000	,0000	,0000	,0000
Median	2,5000	4,0000	5,5000	6,0000	6,0000	6,0000	6,0000	6,0000	6,0000

Fig. 7 – Statistical data of the subgroups A, B, C, D, E, J, K, L, M, O, P, Q, and R.

Controls		N	Mean	StDev	Percentiles (25°	50°	75°)
3 m	P	63	2,19	1,68	1	1	3
	C	74	2,05	1,47	1	2	2
6m	P	60	3,13	1,96	1	3	5
	C	72	2,77	1,68	1	2	4
12 m	P	58	4,32	1,98	2	5,5	6
	C	67	3,98	1,79	3	4	6
2 y	P	53	4,96	1,70	4	6	6
	C	56	5,018	1,64	4	6	6
3 y	P	37	5,21	1,51	5	6	6
	C	44	5,40	1,26	6	6	6

Fig. 8 - Comparison of the perceptual outcomes at the 3-month follow up on congenital hearing loss without progression (C) and progressive hearing loss (P).

Figure 9 shows the statistical results obtained from patients with or without genetic mutations.

As reported in table XI, the most common mutation was the 35delG in the *GJB2* gene. All patients with *SLC26A4* mutations presented bilateral EVA. Note that they had mutations on both alleles. Among these mutations, to our knowledge, 2 have never before described

(Q235R e G557D) and 1 was recently reported in one of our scientific publications entitled "Novel mutations in the *SLC26A4* gene" [55].

Controls		N	Mean	StDev	Percentiles (25°	50°	75°)
3 m	no mut	41	2,09	1,67	1	2	2,5
	mut	35	2,48	1,59	1	2	3
6m	no mut	41	2,82	1,74	1	2	4
	mut	33	3,33	1,84	1,5	3	5
12 m	no mut	40	4,05	1,88	2	4	6
	mut	31	4,54	1,76	3	5	6
2 y	no mut	30	4,90	1,51	4	6	6
	mut	27	5,25	1,58	6	6	6
3 y	no mut	17	5,29	1,40	5	6	6
	mut	23	5,60	0,94	6	6	6

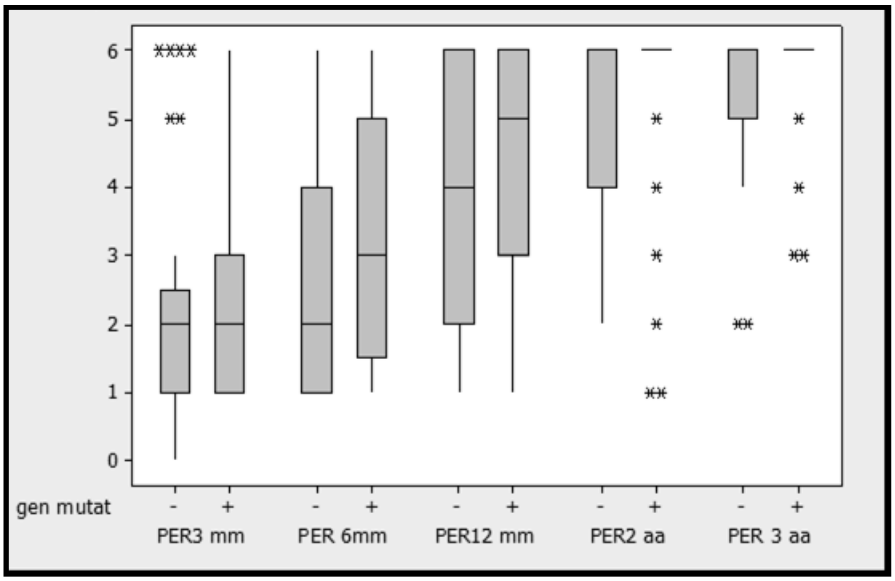


Fig. 9 – Perceptual outcomes at the 3-month follow up on the children who underwent genetic investigation; differences between children with genetic mutations (+= mut) and children without mutations (— = no mut) are shown in the graphs.

GENE	*MUTATION*	*N°*
GJB2	35delG/35delG	15
GJB2	35delG/R184P	4
GJB2	35delG/167delT	1
GJB2	35delG/R143V	1
GJB2	V27I/E114G	1
GJB2	VS1+1G>A/delE120	1
SLC26A4	G209V/Q235R	1
SLC26A4	L445W/G557D	1
SLC26A4	R409H/IVS2+1delG	1
SLC26A4	R409H/Q235R	1
MT-RNR1 (MIT DNA)	C722X (homoplasmy)	1

Tab. XI – Mutations that were found among 143 implanted children.

Controls	N	Mean	StDev	Percentiles		
				(25°	50°	75°)
3 m	20	2,50	1,60	1	2	3
6 m	18	3,55	1,75	2	3	5,25
12 m	18	4,44	1,75	3	5	6
2 y	15	5,13	1,80	6	6	6
3 y	12	5,50	1,24	6	6	6

Fig 10 - Perceptual outcomes of subgroup M (EVA) at the 3-year follow-up

After 3 months of using the cochlear implant, more than half of the patients belonging to the subgroup M (patients who presented EVA) did not achieve the 3th category of perception at the Geers & Moog scale; in the same group, the 50% of the children did not reach the 4th category at the 6-month follow-up, nevertheless they achieved the 5th category 6 months after (1-year follow-up). Only 2 years after cochlear implant activation, the majority of these patients attained a 6th perceptual category at the Geers & Moog scale (fig. 10). There was a statistically significant difference ($p \leq 0.05$) between the control group and the subgroup M (patients who presented EVA) at the 1-year follow-up (Fig. 6).

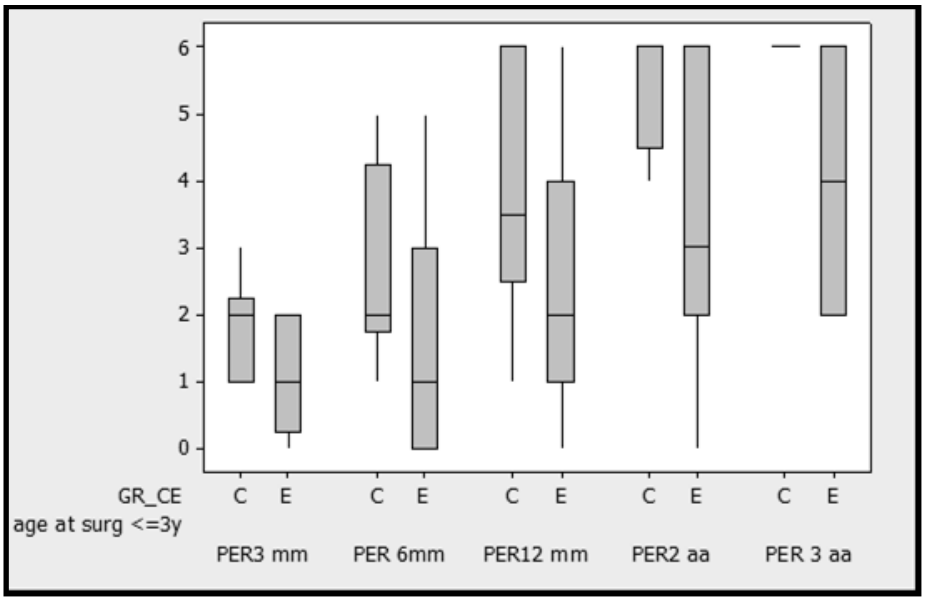


Fig 11 - Comparison between the perceptual outcomes at the 3-year follow-up of children who were younger than 3 years old at the time of surgery and who belong to subgroups C and E.

Given the great importance of timing of surgery for the CI outcomes we compared the results obtained from patients with only malformations of the inner ear (subgroup C) and patients with inner ear and concomitant brain abnormalities (subgroup E); then we divided these patients in those who underwent CI within 3 years of age and those who underwent CI after 3 years of age (Fig. 11-12). Similarly, we compared the patients with only brain abnormalities (subgroup D) and patients with inner ear malformations and concomitant brain abnormalities (Fig. 13-14).

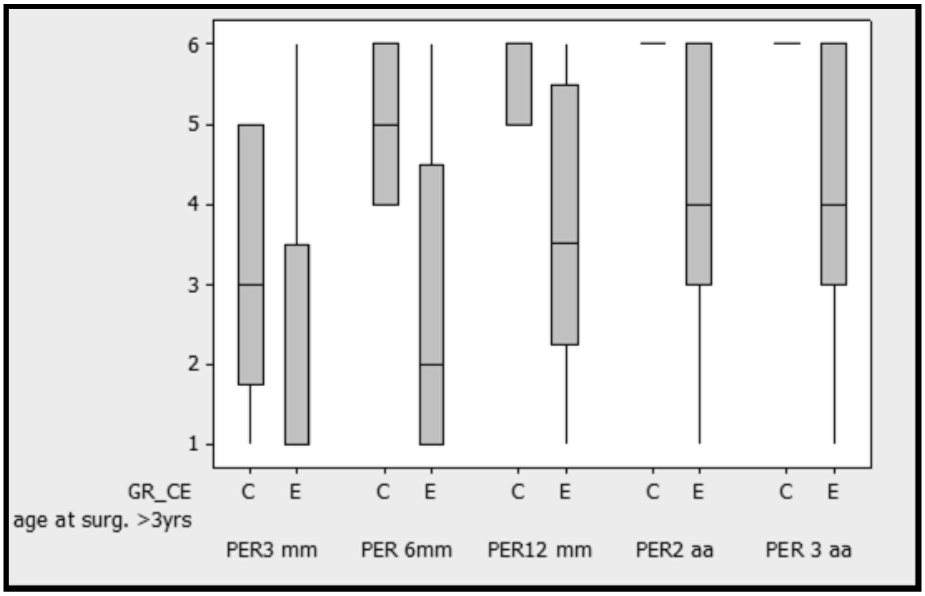


Fig 12 - Comparison between perceptual outcomes at the 3-year follow-up of children who were older than 3 years of age at the time of surgery and who belong to the subgroups C and E.

In our study, it should be noted that the performance after bilateral CI (Fig. 15) can be influenced down by the fact that results were collected starting from the first CI (dragging effect of the second device over the first one) and in case of a delay in the second CI (sequential surgery), the perceptual skills, at the 1-year follow-up, can still be related to the "effect" of the first CI and likely due to differences in time of using the second device. Comparing unilateral CI and bilateral CI (sequential in almost all cases), it was noted that, at the 1-year follow-up, 1 device allowed vowel recognition in closed set tests in 50% of

patients (4th perceptual category), while 2 devices enabled 50% of patients to achieve speech recognition in open set tests (6^ perceptual category).

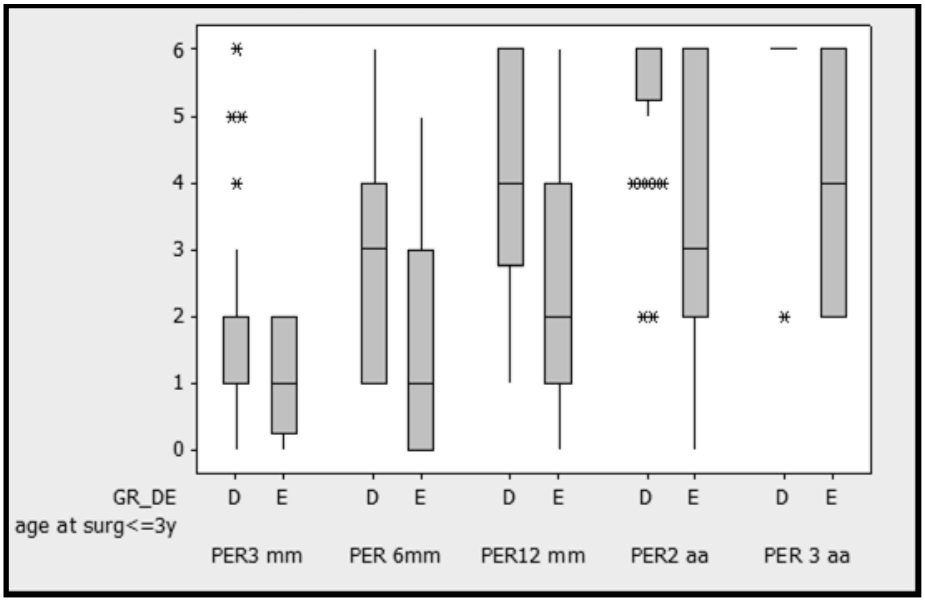


Fig 13 – Comparison between perceptual outcomes at the 3-year follow-up of children who are younger than 3 years of age at the time of surgery and who belong to the subgroups D and E.

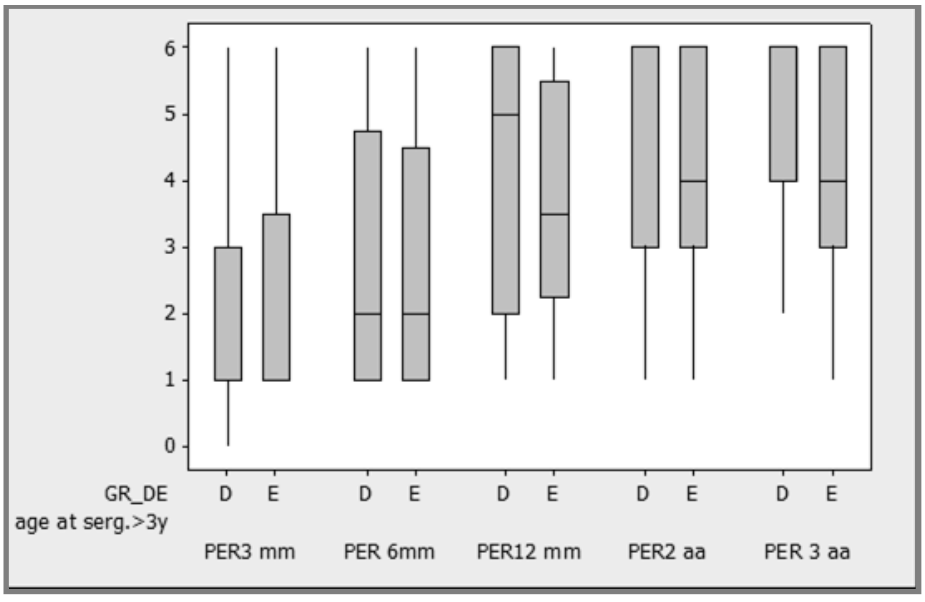


Fig 14 - Comparison between perceptual outcomes at the 3-year follow-up of children who are older than 3 years of age at the time of surgery and who belong to the subgroups D and E.

		1 year follow up			3 year follow up			5 year follow up		
	percentile	25°	50°	75°	25°	50°	75°	25°	50°	75°
Monolateral CI	Main group (n° 123)	2	4.5	6	4.5	6	6	6	6	6
	meningitis (n° 10)	1	2	4	2.5	5	6	6	6	6
	Cytomegalovirus (n° 21)	3	6	6	6	6	6	6	6	6
Bilateral CI	Main group (n° 20)	3	6	6	6	6	6	6	6	6
	meningitis (n° 3)	6	6	6	6	6	6	6	6	6
	Cytomegalovirus (n° 5)	3	5	6	6	6	6	6	6	6

Fig. 15 – Comparison between perceptual outcomes at 1-, 3-, and 5-year follow-ups of children who have 1 or 2 cochlear implants among the MAIN GROUP and subgroups K and L.

More evident was the difference comparing 1 and 2 CI among patients belonging to the subgroup L in terms of rapidity in achieving the higher perceptual categories; in fact all bilateral cases had reached the "open set recognition" at the 1-year follow-up. In the subgroup L, there were 3 patients with post-verbal, simultaneous and bilateral CI (Fig. 15).

4. DISCUSSION

In the present era, when cochlear implantation is a widely accepted therapy for sensorineural hearing loss, the selection of the patients is still a complex issue demanding close collaboration of experts in all different fields. There is no doubt that thorough radiological evaluation is of enormous importance in malformed inner ears. An exact description and, if possible, classification of the abnormality builds the firm base of further evaluation. The results obtained allow us to affirm that abnormalities of the ear and brain are frequent findings among the cochlear implant candidates; for this reason, the neuroimaging has a fundamental diagnostic role. HRCT scans of the temporal bone help to define the surgical anatomy and provide information about cochlear abnormalities that can aid the surgeon in surgical planning and patient counselling. Temporal bone CT scans should be obtained and reviewed for evaluation of cochlear malformation, cochlear ossification, enlarged vestibular aqueduct, and other inner ear and skull base anomalies. An absolute contraindication to cochlear implantation detectable by HRCT is the absence of the cochlea in Michel's aplasia. Although HRCT is the gold standard for evaluating most aspects of temporal bone anatomy, MRI is ideal in imaging soft tissue structures such as the membranous labyrinth and nerves. MRI can identify the presence or absence of fluid within the cochlear turns and the size of the cochlear and vestibular nerves within the internal auditory canals. MRI is superior to HRCT in determining cochlear obstruction due to non-ossified scarring. One disadvantage to using MRI in children, though, is the need for sedation [56].

Patients with severe inner ear malformations are expected to perform more poorly than patients with normal cochlea because of the likelihood of fewer spiral ganglion cells and the more complex surgery in malformed ears. Nevertheless, different types of electrode arrays have been introduced to improve the placement of device and to develop speech

performance. Because the electrodes may not be confined by scalar anatomy, electrode migration may occur, and individuals with cochlear malformations may require frequent reprogramming of the electrodes. Electrodes that are not intracochlear or that elicit facial nerve stimulation can be eliminated from the "map" as can electrodes that elicit facial nerve stimulation in implanted normal cochleae.

In previously published papers, several authors have shown that the benefits of implants in malformed inner ears are comparable to those gained by deaf children with morphological normal ears [13,36,38,57,58]. Indeed assert that cochlear implantation can be successfully performed in children with inner ear malformations. The various types of inner ear malformations may have quite different prognoses for good auditory performance. In cases of cochlear ossification, the functional effects remain especially controversial. Predictors of good performance include the constellation of incomplete partition of cochlea: enlarged vestibular aqueduct (EVA), dilated vestibule (i.e. Mondini's malformation), isolated EVA and partial semicircular canal aplasia. These patients achieve a different level of open set recognition in over the 80% of cases. Children with other cochlear dysmorphologies such as the common cavity or with associated pathologies like the CHARGE association and psychomotor retardation–developmental delay can have poor performance after implantation. Obtaining knowledge of cochlear malformation is especially important in counselling parents before implantation [36].

Kim et al. [13] observed that cochlear nerve hypoplasia was responsible for poor CI outcome, that reduced the chance of an acceptable development of perceptual and linguistic capabilities. Other malformations can be responsible for delay in reaching the higher categories at the Geers & Moog scale. Nevertheless, they found no significant differences between the study group (with inner ear malformations) and control group (without inner ear malformations) at the 2-year follow-up. Loundon et al. [38] reported similar results, that are

summarized as follows: (1) at the 12-month follow-up, 83% of children achieved 75% of speech recognition in closed-set tests (corresponding to the 5th category at the Geers and Moog scale); (2) only 16% of those patients had obtained the same results during pre-operative tests; (3) at the 2-year follow-up, they improved the perceptual abilities and (4) 64% of children achieved 50% of speech recognition in open-set tests (corresponding to the 6th category at the Geers and Moog scale).

Eisenman and colleagues found that all the subjects of their study showed improved performance on all measures of speech perception over time. Overall, the two groups showed no statistically significant differences in performance at 6 and 24 months. However, subjects with malformed cochleae evidenced slower rates of improvement than did their matched control subjects. Subjects with more severe malformations demonstrated poorer performance, but this may have been attributable to preoperative factors rather than to implant performance [57].

Incesulu and colleagues say that except cochlear or cochleovestibular nerve agenesis, inner ear malformations cannot be accepted as a contraindication for cochlear implantation. Although there can be difficulties during the surgery or in the postoperative period, patients with inner ear malformations can also benefit from cochlear implantation. It is essential that all possible complications and postoperative performance should be discussed with the parents [58].

Although there is controversial data in the literature on the prognostic value of specific factors, such as cochlear malformations and brain abnormalities, we can conclude that these factors do not necessarily affect the outcome of the cochlear implant; in fact, most of the factors that are typically encountered achieve satisfactory results. With the exception of a few special cases, such as stenosis of the internal auditory canal (<2 mm) and the common cavity, or instead the lack of the modiolus, which prevents an optimal pairing between

electrodes and cochlear nerve fibres, the results, especially over a long-term period, are comparable to patients without neuroimaging findings, in terms of the achievement of perceptual abilities.

However, we must stress that, especially in the short term period (12 months), the presence of cochlear malformations could slow the attainment of more complete perceptual abilities; even more evident is the effect in the presence of disorders of the central nervous system. Note that the simultaneous presence of the inner ear malformations and anomalies of the brain determines a negative synergistic effect, with the achievement of lower perceptual categories (according to the Geers & Moog score) for the same period of use of the cochlear implant.

In the present study, 28% of implanted children were affected by brain anomalies identified by pre-operative neuroimaging. Our results compare well with similar studies. Trimble et al. found central MRI abnormalities in 40% of the patients in their group compared to 20% in the study performed by Lapointe et al. [30]. Lapointe emphasized the importance of neuronal migrational delays resulting in the neurodevelopmental delay and potentially poor outcome from cochlear implantation. In addition to the brain MRI findings mentioned helping to predict speech perception and language outcome Trimble et al. also commented on the importance of some findings to the anaesthetist (ventriculomegaly, hydrocephalus, Chiari malformation and intracerebral haemorrhage) [28]. Of the abnormalities detected, 49% were related to known pre-existing conditions. By far the most common abnormality detected in 84 patients was white matter changes (70%) and this was found in 13% of all patients investigated. Frequently the white matter changes were related to previous conditions/insults and included infection, ischaemia, hypoxia and prematurity.

Apart from diagnosing incidental findings, MRI brain can aid in the diagnosis of hearing loss and has been shown to be important in predicting language and speech perception outcomes

in patients with kernicterus and Cytomegalic virus (CMV) infection as etiological factors [29,59]. White matter changes have been shown to be an important determination of abnormal neurodevelopmental outcome and might help predict future problems (seizures and intellectual impairment) in certain patients [60.]. The full role of white matter changes in predicting hearing outcome in cochlear implant patients is still unclear.

A further potential advantage of pre-operative brain MRI is that it might identify pathology that can be followed up with CT imaging, which is easily accessible post cochlear implantation. This was the case in three of the patients in this series with a lipoma, a hamartoma and a pinealoma diagnosed on brain MRI whom required further imaging after cochlear implant. In addition brain MRI will also provide a baseline for comparison with future MRI scans.

The group of patients with bilateral implantation was very heterogeneous by virtue of the great variability in the time of execution of the second cochlear implant; thus, it was not possible to determine the effect in the subgroups. We have focused the investigation on those patients with meningitis and cytomegalovirus infection because the number of cases available for comparison was higher and more homogeneous. Either subgroups (K and L) show a significant improvement after 1 year after the activation of the second cochlear implant.

In children, the most likely cause of cochlear ossification is meningitis. Twenty per cent of children acquire profound bilateral sensorineural hearing loss prior to the age of 3 years; 90 per cent of these cases are meningitic in origin.[61] Labyrinthitis ossificans results from severe inflammation of the inner ear and can be associated with a variety of pathology (advanced otosclerosis, viral or bacterial labyrinthitis, and autoimmune inner ear disease). Labyrinthitis ossification presents one of the greatest challenges to effective, safe cochlear implantation. Green and colleagues demonstrated that ossification due to meningogenic

labyrinthitis extended further into the cochlea than ossification due to other causes. The extra bone growth makes the insertion of the electrode a difficult process [62]. In addition, the stimulation of surviving neural elements may be compromised by the bony obliteration, and histopathololgic reports have shown an association between the degree of bony occlusion and a decreased number of surviving spiral ganglion cells, particularly in cases of bacterial meningitis[63]. For these reasons, patients with labyrinthitis ossificans were often thought to perform at lower levels than those without ossification. In previously published papers [64,65], several authors have shown that that children with postmeningitic hearing loss and cochlear ossification could attain significant benefit from their implant, although children without ossification were likely to perform better. A key factor for success may be the timing of implantation. Ossification may appear as early as 2 months following meningitis, leaving a small time period during which electrode insertion is optimal. As mentioned previously, however, central nervous system sequelae of meningitis are likely to hold sway in determining outcome [66].

Hearing loss is the most common manifestation of congenital CMV infection making CMV a leading cause of nonhereditary congenital hearing loss [67.]Cytomegalovirus (CMV) is one of the most common congenital viral infections. The manifestations of CMV infection cover a broad spectrum ranging from asymptomatic to severe systemic disease resulting in significant morbidity and mortality. 90% of infants with congenital CMV are asymptomatic at birth. Despite being asymptomatic at birth, up to 7% of these children will develop sensorineural hearing loss that can be unilateral or bilateral, fluctuating or progressive, and range from mild to profound [68]. Approximately 10% of infants with congenital CMV are symptomatic at birth, and 40% of these patients will develop sensorineural hearing loss [69]. Given the relatively large number of children potentially affected by CMV-related hearing loss and the wide range of manifestations of congenital CMV infection, it is difficult to

predict how a child with symptomatic CMV will perform with a cochlear implant. Congenital CMV infection accounted for a significant proportion of patients with SNHL, with an incidence rate comparable with that of *GJB2*-related SNHL.

Previous studies have shown that brain imaging may be a good predictor of adverse neurodevelopmental outcomes. In a study of children with a diagnosis of SNHL, 80% of the CMV positive children had abnormal brain MRI scans compared with only 33% of CMV negative children [70]. Our study demonstrated that certain imaging findings may correlate with worse outcomes after CI. Interestingly, the location of the abnormalities also seemed to correlate with worse perceptive outcomes. The majority of the abnormalities were found in the temporal lobe and parietal lobe. The parietal lobe processes sensory information and houses our language abilities, and the temporal lobe regulates emotion, hearing, language, and learning, which could explain why language outcomes are poorer in children with abnormalities in these regions.

Children with symptomatic congenital CMV appear to derive benefit from CI albeit at a slower rate. In a study of 13 children with symptomatic congenital CMV, 73% of implanted children achieved closed-set word recognition, and 63% achieved open-set word recognition[29]. Ramirez Inscoe and Nikolopoulos demonstrated mixed results for speech perception and intelligibility with 50% of children with congenital CMV performing more poorly than controls, 31% performing similarly, and 19% performing better than controls These children did, however, derive auditory benefit from cochlear implant. [71].

Although our study has limitations including its retrospective nature and small sample size, it provides data that may further efforts to identify factors which may help predict which children with congenital symptomatic CMV will benefit from CI, albeit at a slower rate than other children. The location of central nervous system abnormalities, including gliosis and calcifications, may play a role in audiometric and perceptive outcomes after CI.

Early measurements such as brain imaging findings and internal ear imaging findings may allow for more accurate counselling of families regarding anticipated post-implantation performance in children with symptomatic congenital CMV.

Cochlear implants can have impressive effects on a child's language abilities, yet outcomes remain variable across the paediatric population. Numerous studies have thus attempted to identify predictors determining post-implantation communication. So far, relevant factors are age at onset of deafness, age at implantation, length of implant use, amount of residual hearing, duration of deafness, educational mode and resources, and psychosocial elements.

A clear factor seems to be the age at implantation: children appear to perform better when implanted at earlier stages.[72] On IT-MAIS testing, Robbins and colleagues found that children implanted under the age of 19 months demonstrated faster progress and higher scores than those implanted between the ages of 2 and 3. As Geers found, though, this age advantage disappears after 2 years, implying a critical period of development within the first 2 years of life. At older ages, then, other factors begin to affect implant performance [50].

Although it is known from the literature that the precocity of diagnosis and treatment is an important prognostic factor in the auditory / habilitation, in our study the difference between the patients that, at the time of surgery, were younger than 3 years of age and those who were older than 3 years was not significant or at least fell short of expectations. More specifically, children who received implants within 3 years of age showed the worst results in the early controls (3 months); we cannot exclude a bias of the study due to the fact that children implanted at an early age, at three months after the implant activation, are not able to express perceptual skills that were included in the classification that was used. Nevertheless, at the 6 month follow-up, they started to show the "overtaking" effect in their

perceptual performances. The outcome is not significantly different between the two groups, starting from the 1-year follow-up.

Paediatric audiological services should offer children with sensorineural hearing loss testing for mutations in Connexin proteins because mutations in at least two Connexins have been implicated in nonsyndromic hearing (*GBJ2* and *GBJ6*). As mentioned above, the most frequent mutation is found in Connexin 26 encoded by the *GBJ2* gene (35delG), resulting in DFNB1 [73]. Mutations in Connexin 26 result in sporadic and familial severe/profound prelingual hearing loss [20] and account for about 50% of recessive and 10% to 25% of sporadic nonsyndromic hearing loss in Southern European children. An evaluation from United States has shown that nearly 30% have Connexin 26–related hearing loss with all degrees of hearing loss [73] and thus it can be stated that mutations in Connexin 26 may result in all degrees of hearing loss. Thus, it is recommended that all children under 18 years of age with bilateral, permanent, nonsyndromic sensorineural or mixed hearing loss, irrespective of the level of impairment, for which there is no other explanation, should be offered testing. The initial testing should check for 35delG and/or the other most frequent mutations in the background population. Unless the first screening identifies mutations on both alleles, testing should go on to screening of the entire coding region and splice sites for mutations. In addition, the presence of *GBJ6*/Cx30 deletions should be sought.

The perception at 3, 6, 12, 24, and 36 months shows no significant differences between subjects with genetic mutations (35delG in almost all cases) and patients without mutations. However, the obtained results show how the concomitant presence of malformations of the inner ear in the group of patients with mutation moves away from the expected outcome in patients with the same mutation but without abnormalities of the inner ear. The percentage of patients with mutations in our study group does not differ from the rates observed among patients without neuroimaging findings. This finding means that we are still far from

establishing the true contribution of DNA mutations on the anatomy and development of the ear and brain. Therefore, it can be concluded that the detection of an abnormality of the ear or brain should not prevent the execution of genetic testing for mutations that are known to be those that are not associated with malformations (e.g., mutations in the gene *GJB2*).

As part of the protocol for diagnostic evaluation imaging techniques should be used in order to detect aplasia/hypoplasia and/or malformations such as enlarged vestibular aqueduct (EVA). EVA is often found in subjects with Pendred syndrome that is a recessive genetic hearing disorder. The gene responsible for Pendred syndrome has been located to chromosome 7q31 and designated *PDS (SLC26A4)*. The gene product, pendrin, is a transmembrane chloride-iodide cotransporter protein, probably essential for endolymphatic homeostasis. Sensorineural hearing loss may be fluctuant or progressive, ranging from mild to profound. The diagnosis of Pendred syndrome (or DFNB4) in such cases depends on analysis of mutations in the *PDS* gene, where the most frequent mutation is the *SLC26A4* [55]. An enlarged vestibular aqueduct remains the most common malformation of the inner ear, but it does not appear to influence the outcome of the cochlear implantation.

There were no significant differences between the group of children who had congenital profound hearing loss and children with progressive hearing loss, in either the short- or the long-term period. Comparing the perceptive outcomes of subgroups C (with inner ear malformations) and E (inner ear malformations with brain abnormalities) shows a significant difference starting from the 6-month follow-up ($P < 0.05$), which becomes more and more evident over time (at a 2- and 3-year follow-up, $P < 0.01$), in favour of those subjects who have only malformations of the inner ear and who have better performances.

We also compared the outcomes of the subgroups D (brain anomalies) and E (inner ear malformations with brain abnormalities) and, in this case, the differences begin to emerge at 12 months from the cochlear implantation ($P < 0.05$); they become more significant over time

(at a 2- and 3-year follow-up, $P < 0.01$), in favour of those that have only brain anomalies that have better performances.

Brain anomalies affect the long-term outcome after cochlear implantation the most, especially among children who were older than 3 years of age at the time of surgery; comparing those children who belong to subgroups C and E showed an increasingly significant difference starting from 6 months ($P < 0.05$) after the cochlear implant activation. Furthermore, children who were older than 3 years of age and who belonged to subgroups D and E did not show any significant difference, from the underlying "dominant effect" of the brain abnormalities. This "dominant" effect appears to be less evident among the children who are younger than 3 years of age at the time of surgery, probably due to the greater neuronal plasticity.

5. CONCLUSIONS

A cochlear implant is a relatively safe and effective treatment for patients who have inner ear malformations and abnormalities of the brain. The aetiology remains unknown in most cases (18.9%). The cytomegalovirus infections are the main form of acquired deficit. The genetic mutation that is the most common among patients in this study remains the 35delG *GJB2* gene. The EVA is still the most common malformation of the inner ear, but it appears to have no specific effect on the outcome of the cochlear implant.

Gliotic injuries and disorders of the white matter brain abnormalities were more frequent, which in general showed a dominant effect on the outcome that was negative. Especially difficult is fitting the result and the outcome of patients with stenosis of the internal auditory canal or in the presence of malformations with the cochlear absence of the modiolus.

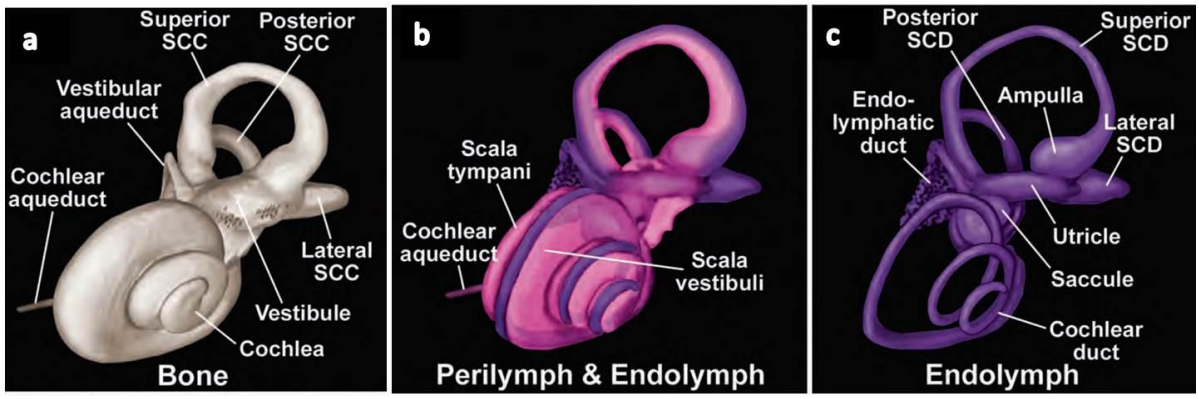
Neuroimaging has been vital for a correct diagnosis and proper pre-operative evaluation of cochlear implant candidates. Furthermore, the obtained data could be useful in defining the most appropriate timing of the follow-up, in specific cases and, if necessary, to develop better rehabilitation strategies in the event that the outcomes differ from the expected outcomes.

The CI outcome depends on many variables that range from the age at the time of the surgery to the communication mode. Nonetheless, before demanding a multidisciplinary approach, the otologist (or audiologist) has the responsibility to verify the correct functioning of the device, requiring, if necessary, a manufacturer's report to rule out technical failure. Afterwards, a clinical team should manage such unsatisfactory performances, after CI, starting from a self-review process of the applied paths (in terms of auditory rehabilitation or speech training), in order to detect errors in their settings. If there are persisting doubts concerning with the CI results after a technical and methodological

review for challenging cases, the first functional and aetiological diagnosis should be reconsidered and re-evaluated by a multidisciplinary team.

Cooperation between parents, school administrators, teachers, and speech specialists is also vital to the success of the child.

Although further studies are necessary for the identification of predictive factors, especially in challenging cases, the results of the present study have confirmed the need to carry out diagnostic, therapeutic and rehabilitation processes in specialised centres with extensive and proven experience.



Lane J, Witte RJ. *The Temporal Bone: An Imaging Atlas*. Springer 2010

Fig. 16 – The inner ear. Right anterior oblique views of 3D reconstructions from microscopy data sets. (**b**) Micro CT reconstruction of the bony labyrinth. (**c**) Micro MR reconstruction of the membranous labyrinth to include the perilymphatic and endolymphatic spaces. (**d**) Micro MR reconstruction of the endolymphatic structures of the membranous labyrinth only. Note the anterior position of the scala vestibuli and the posterior position of the scala tympani within the cochlea [74]

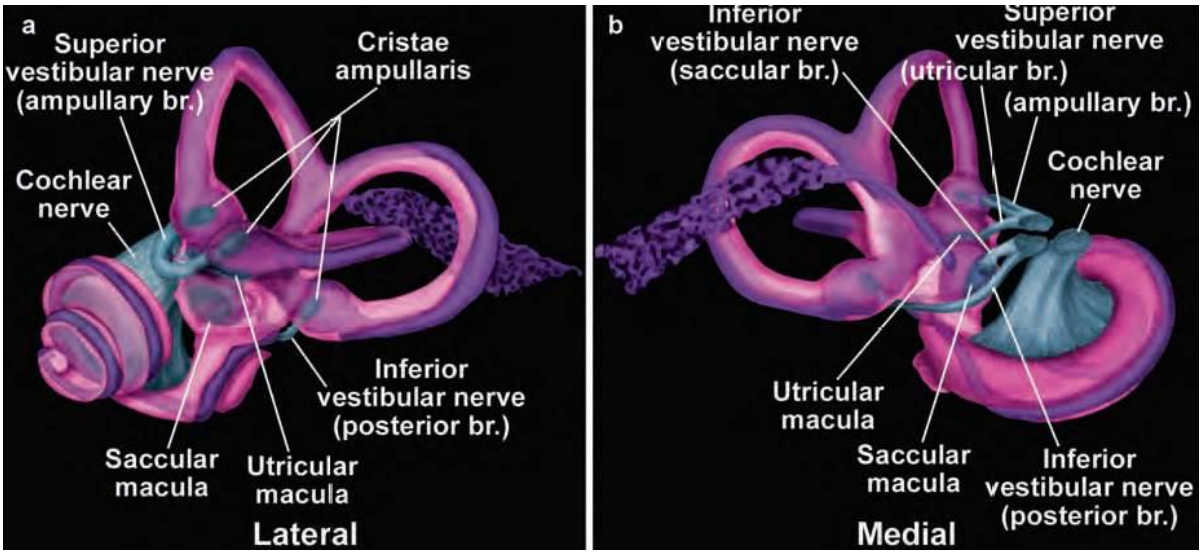


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Fig. 17 – Innervation of the inner ear. (**a**) Lateral and (**b**) medial views of the membranous labyrinth. Superior and inferior vestibular nerves innervate the vestibular apparatus and the cochlear nerve innervates the auditory apparatus of the cochlea.

The cochlear nerve is composed of efferent fibers from all the spiral ganglia cells found at the base of the spiral lamina. They arborize through multiple small channels within the modiolus and coalesce within the cochlear nerve aperture at the apex of the internal auditory canal (IAC). Spiral ganglia cell afferent fibers transmit input from the hair cells of the organ of Corti within the cochlear duct (scala media)

Note that the superior vestibular nerve has an ampullary branch supplying the cristae ampullaris of the superior and lateral semicircular ducts and a utricular branch supplying the utricular macula. The inferior vestibular nerve has two branches, the saccular branch innervating the saccular macula, and the posterior branch, innervating the crista ampullaris of the posterior semicircular duct. [74].

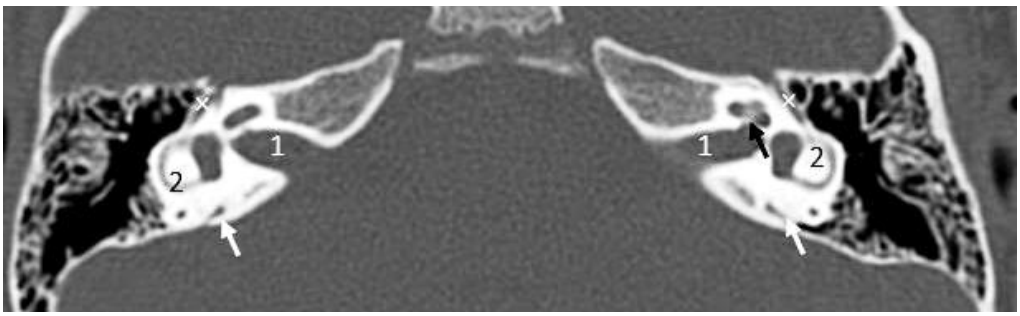


Fig. 18 - Normal ear, CT scan, axial image: 1 = internal auditory canals; 2 = lateral semicircular canals; white arrows = vestibular aqueducts; black arrow = cochlea (modiolus); white X = facial nerves.

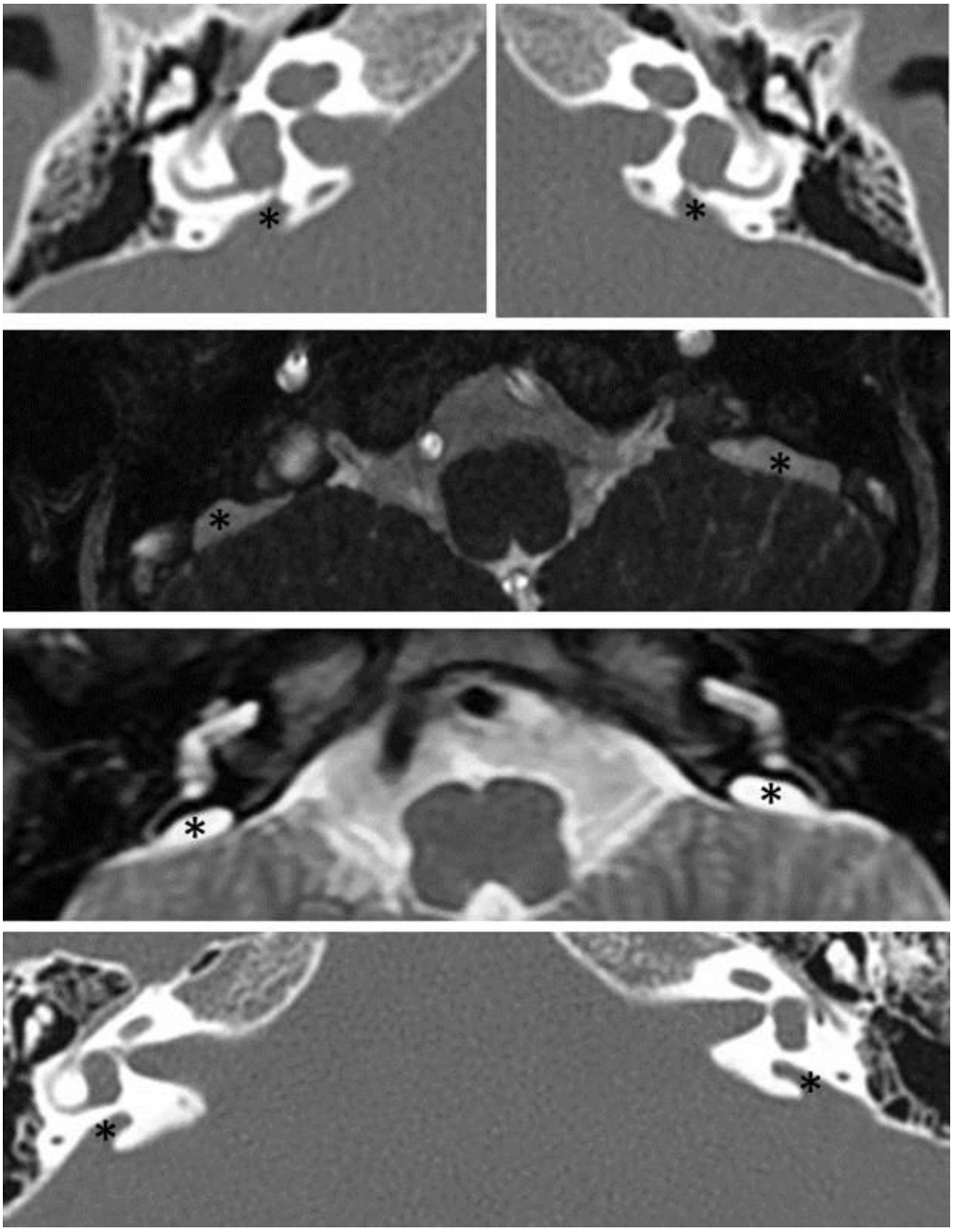


Fig. 19 - CT and MRI temporal bone; black asterisks = enlarged vestibular aqueduct (EVA).

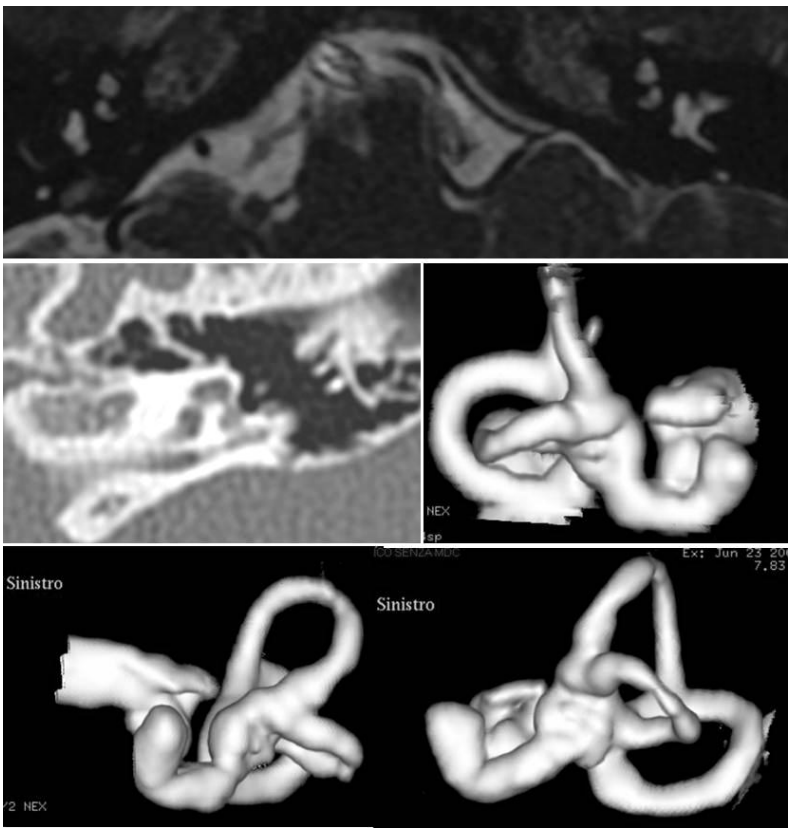


Fig. 20 - CT and MRI temporal bone scans with 3-D MR imagines showing bilateral hypoplastic cochlea with normal basal turn.

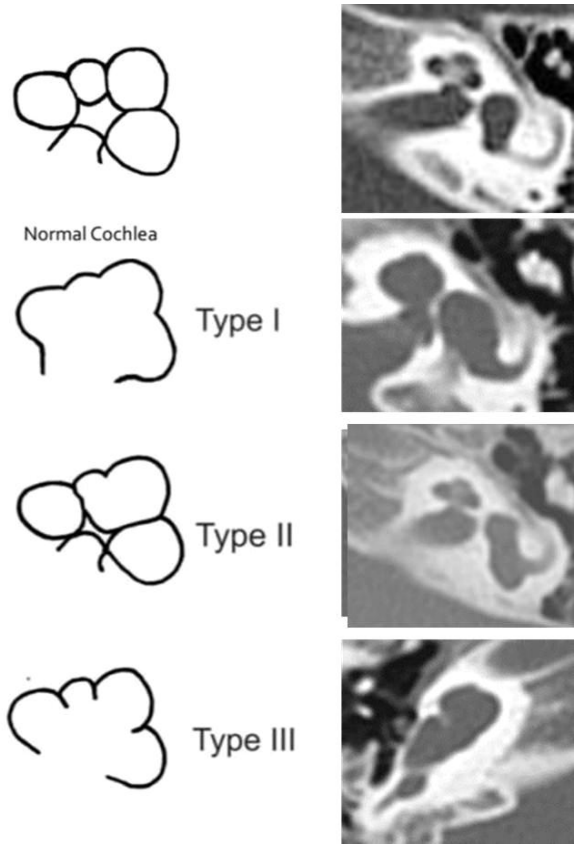


Fig. 21 - Incomplete Partition Types [45]

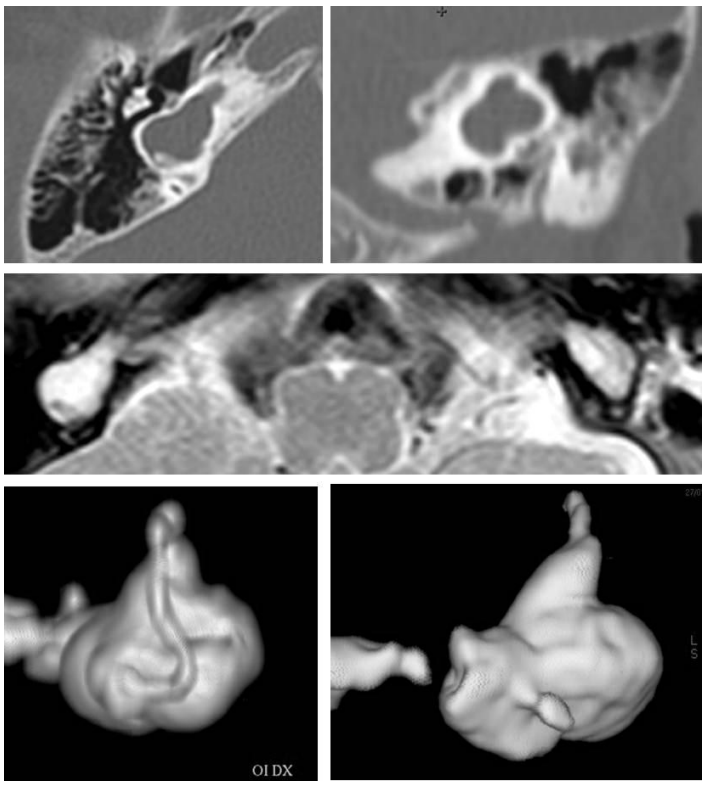


Fig. 22 - CT and MRI temporal bone, 3-D MR imagines. The bony labyrinth presents as one large cystic structure without differentiation of the cochlea or the semicircular canals, there are only small bud like recesses anteriorly and posteriorly shown, common cavity.

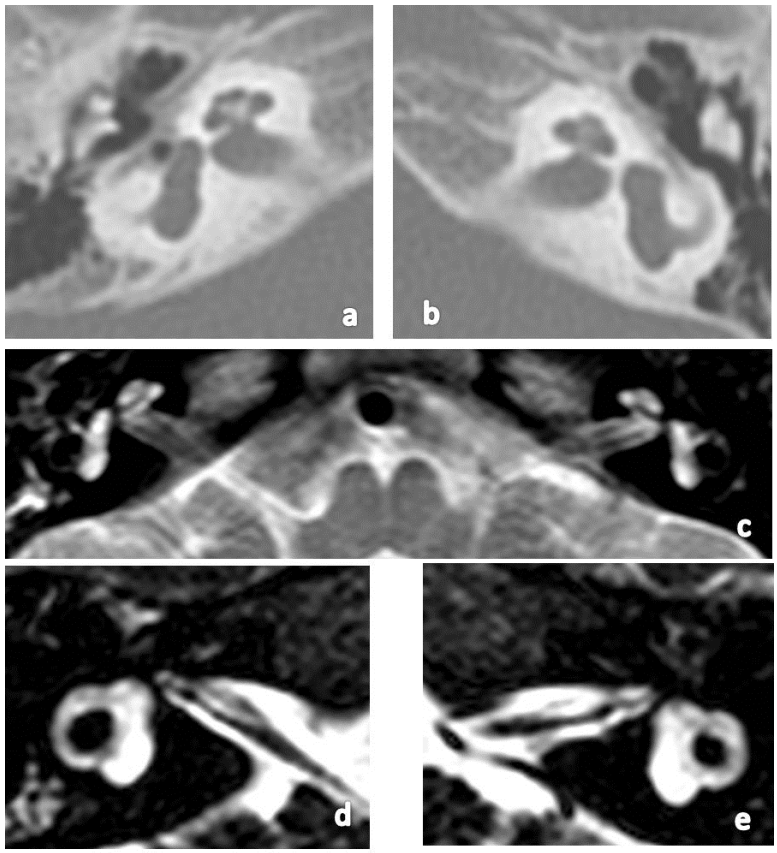


Fig. 23 - CT and MRI temporal bone. Hypoplastic cochleae and dilated saccules**.**

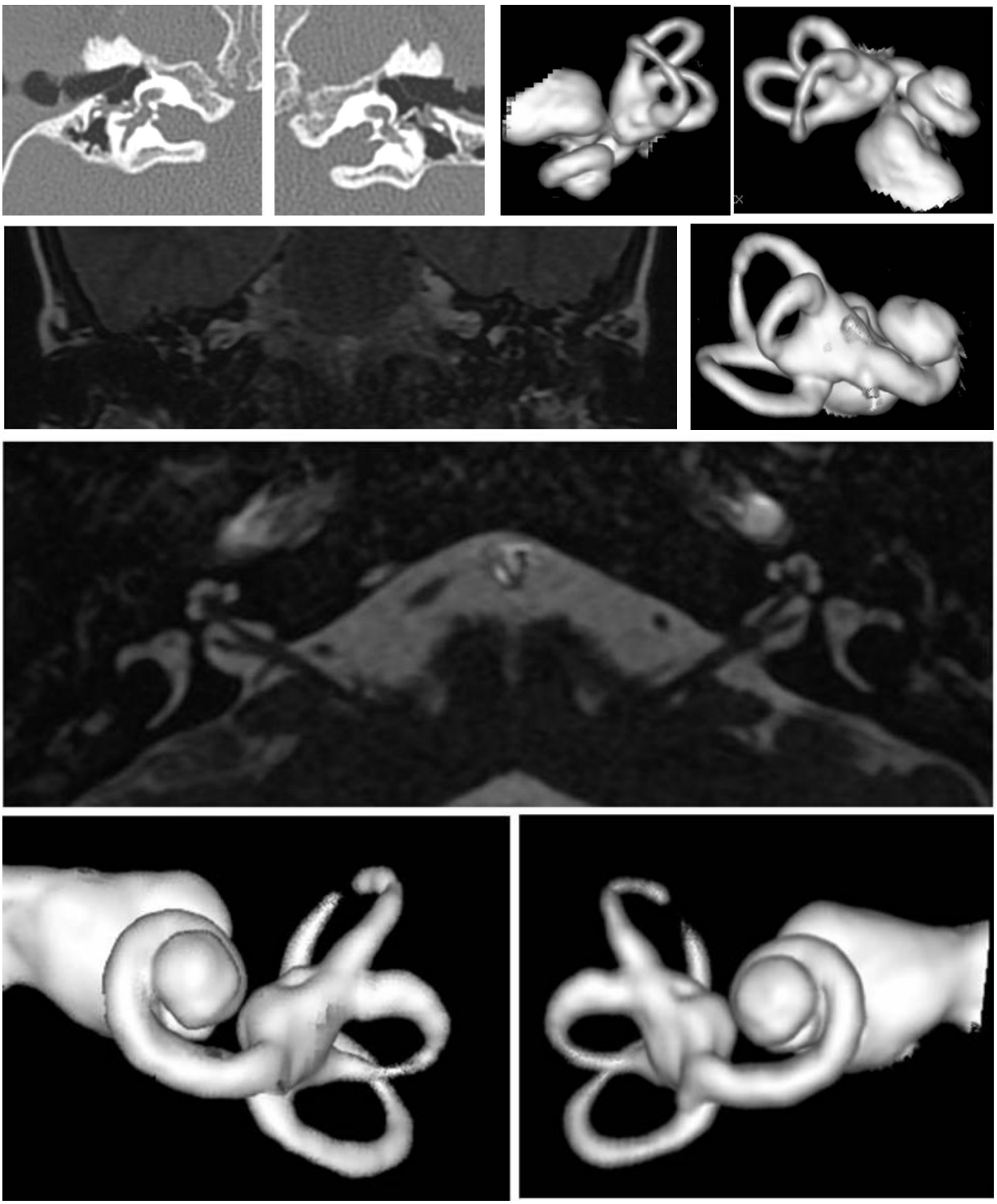


Fig. - 24 CT and MRI temporal bone, 3-D MR imagines; bulbous dilatation of the fundi of the internal auditory canals and congenital stenosis of superior semicircular canals.

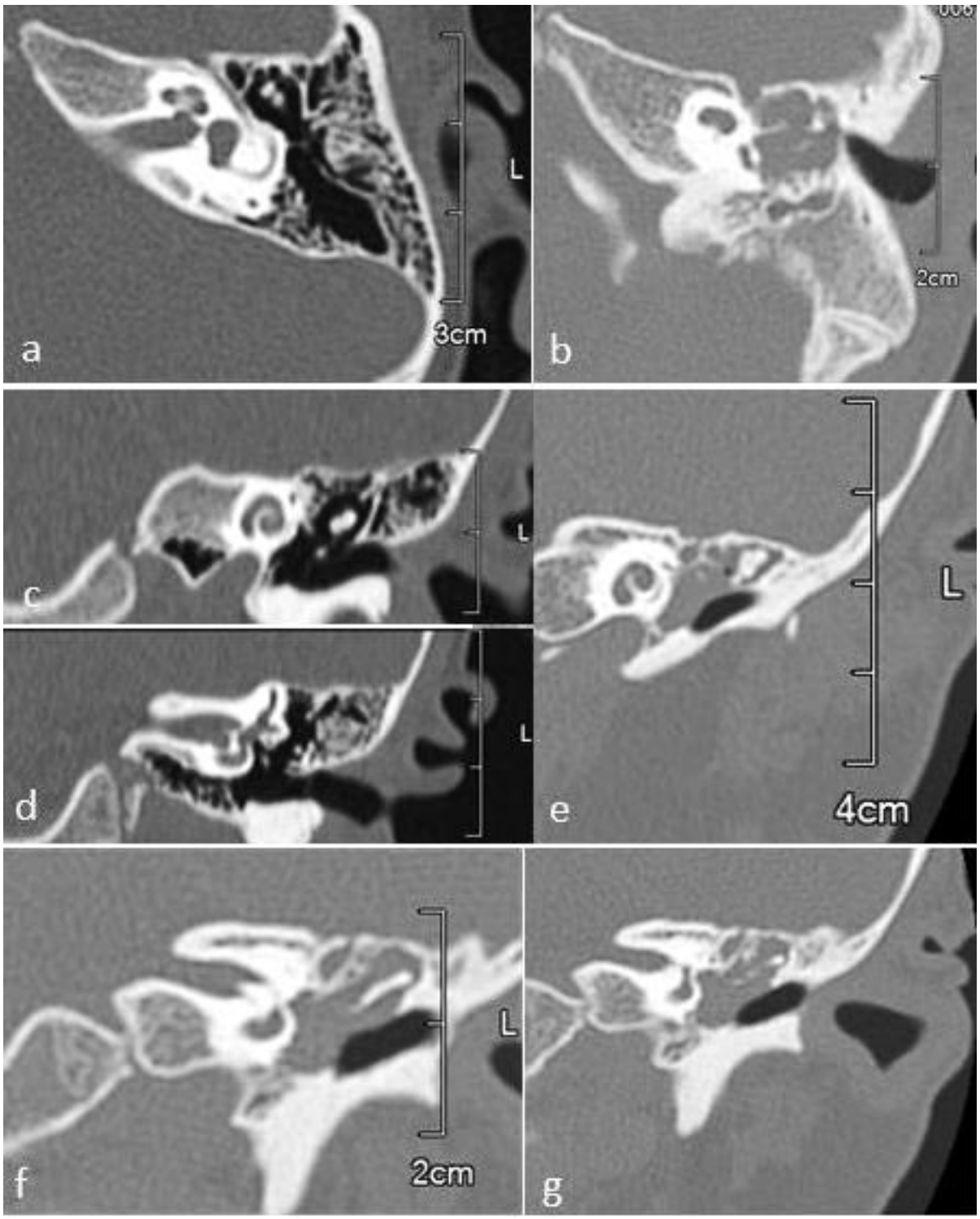


Fig. 25 - Temporal bone CT scan - Axial and coronal images: a), c), d), normal ear; b) hypoplastic/cystic cochlea, modiolus absent, anomalous facial nerve course, absence of the vestibular system; c) malformed and dislocated ossicular chain, cochlear malformation (hypoplasia); f) g) absent semicircular canals.

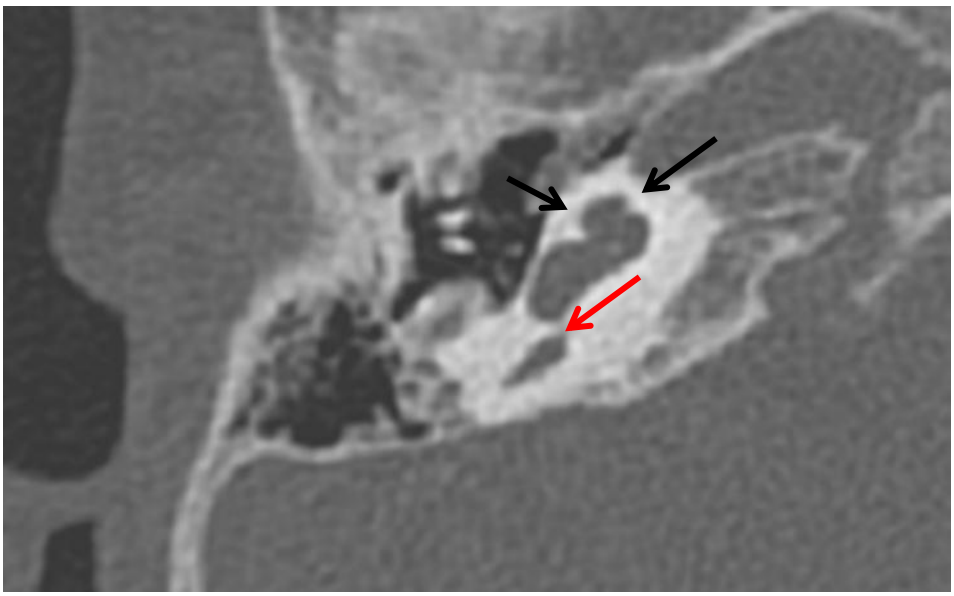


Fig. 26 - Axial CT scan showing an incomplete partition type III (black arrows) and cystic aspect of the vestibular system (red arrow).

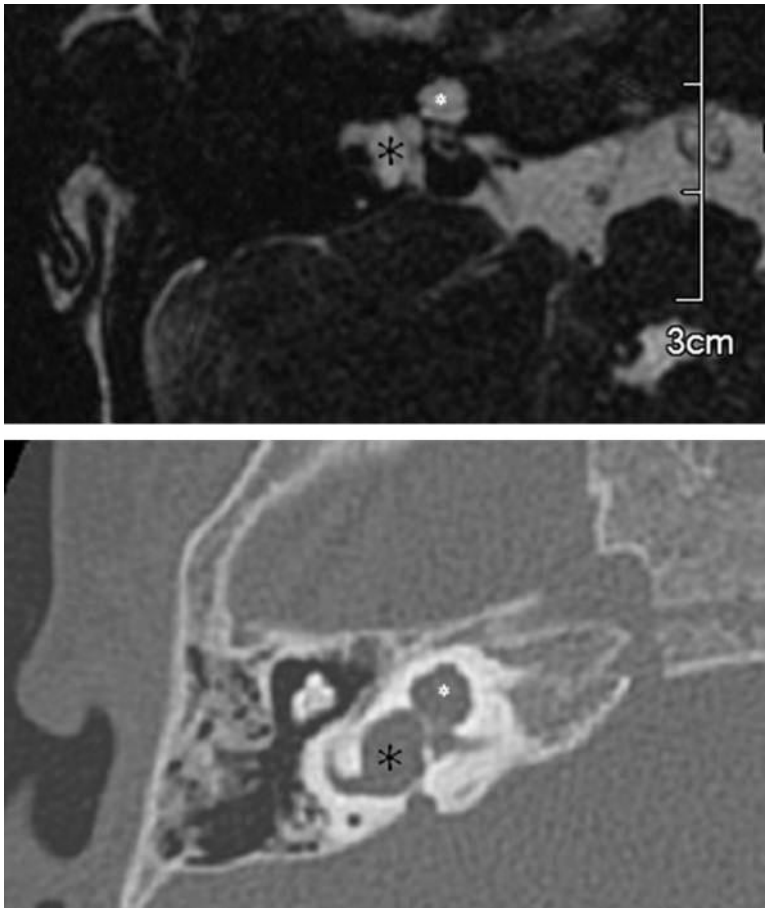


Fig. 27 - MRI and CT scans of temporal bone (right ear) revealing a cystic cochlea (white asterisk) and dilated vestibule (black asterisk).

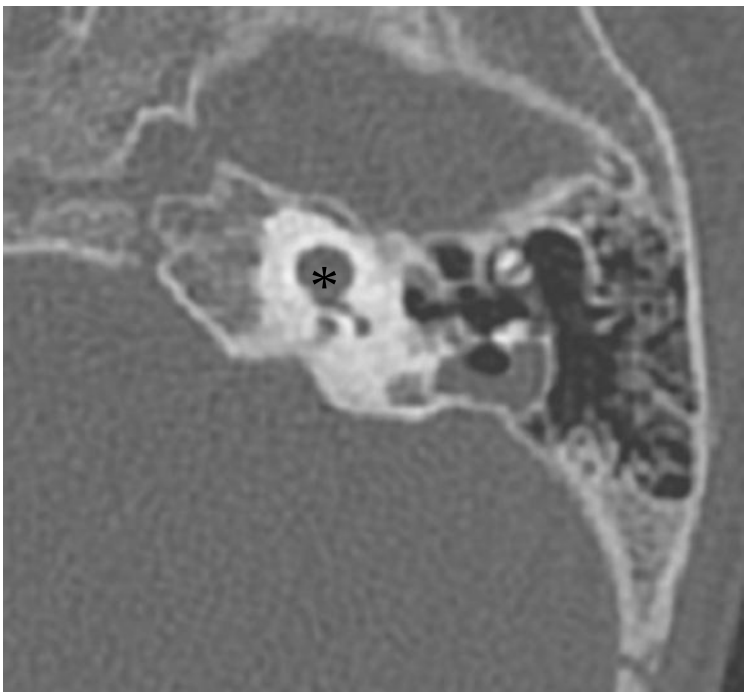


Fig. 28 - CT scan, axial image of temporal bone: incomplete partition type I.

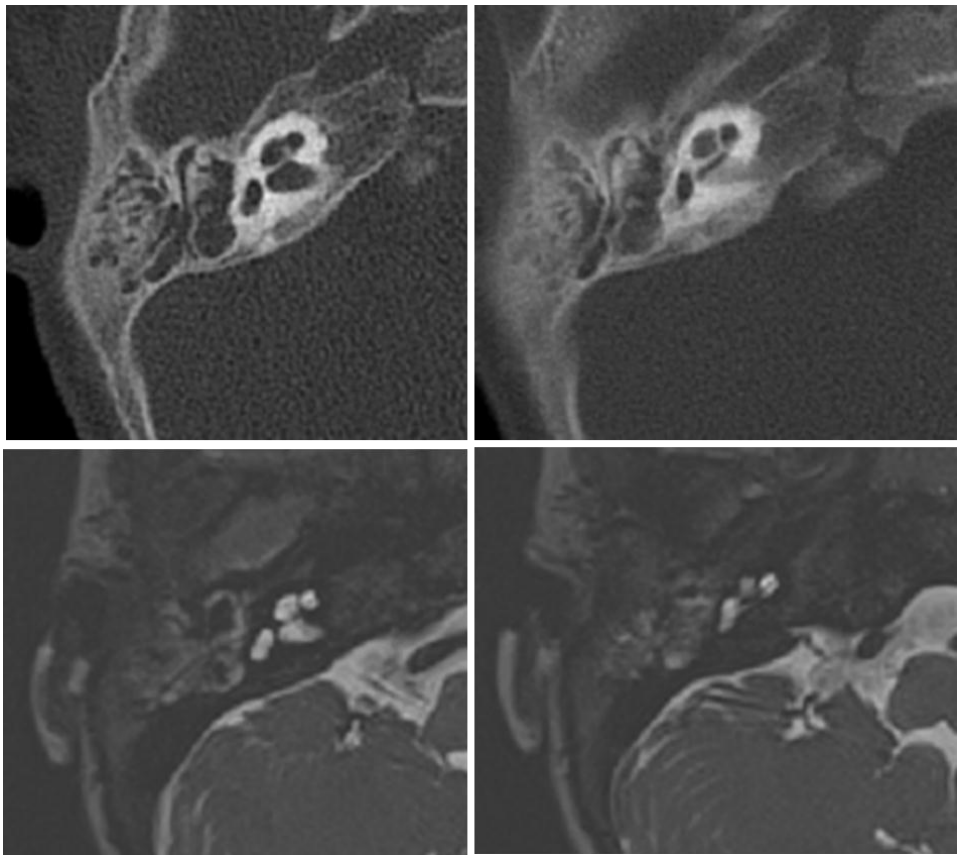
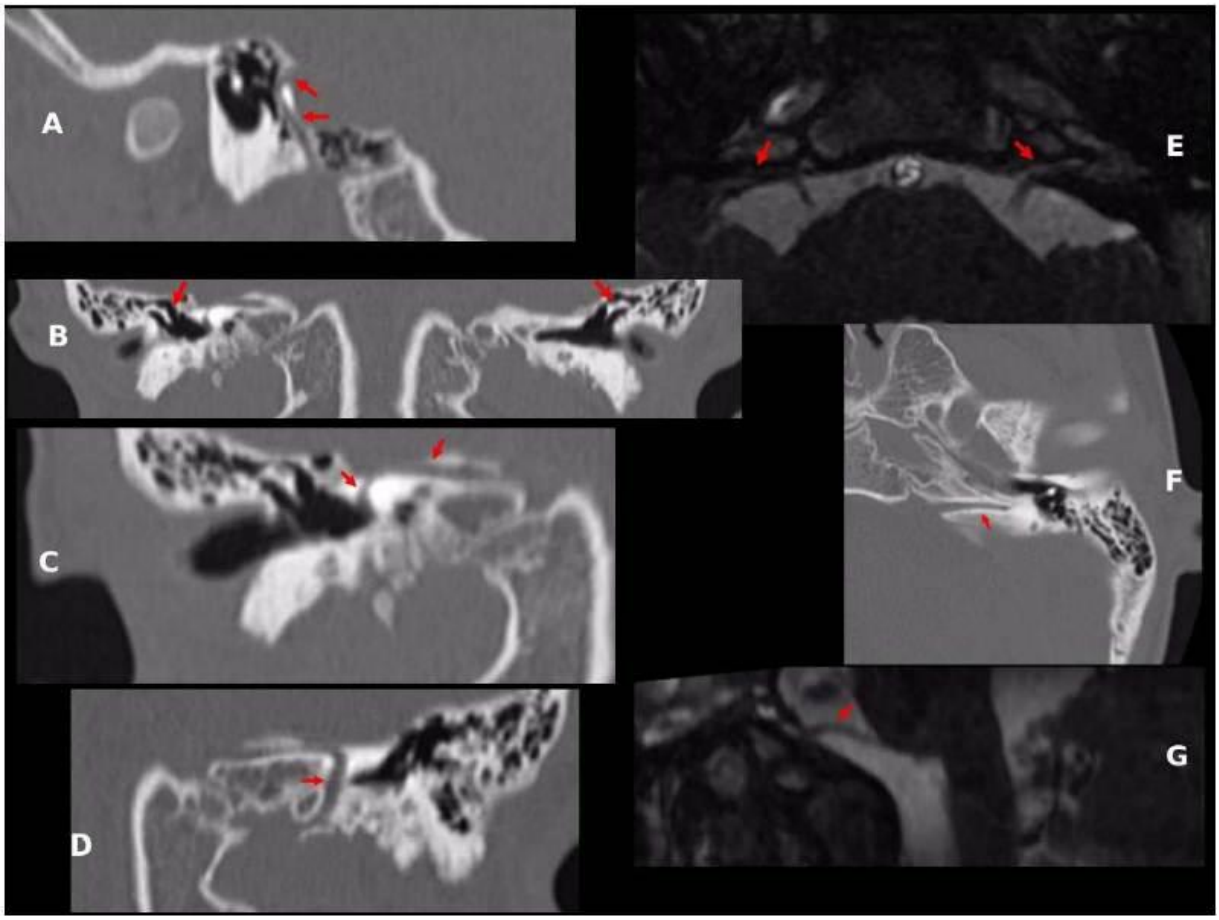
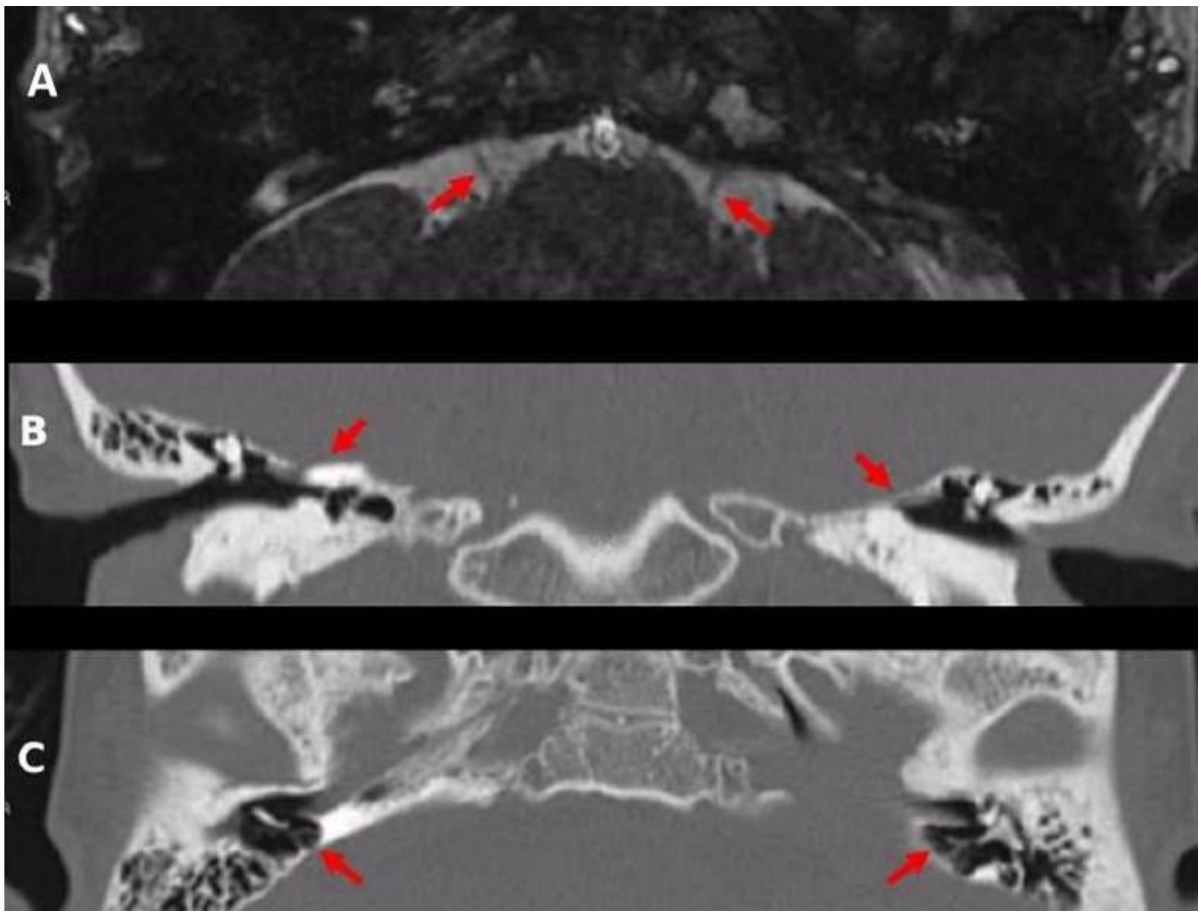


Fig. 29 - CT and MRI revealing an incomplete partition type II in a patient affected by CHARGE association.



Sensi A, Ceruti S, Trevisi P, Gualandi F, Busi M, Donati I, Neri M, Ferlini A, Martini A. LAMM syndrome with middle ear dysplasia associated with compound heterozygosity for FGF3 mutations. Am J Med Genet A. 2011;155A(5):1096-101.

Fig. 30 - LAMM syndrome (A) CT scan. Second bend and vertical tract of the right facial nerve. (B) CT scan. On the both sides are evident hypoplasia of incus and aplasia of staple. (C) CT scan. First and second intracanalicular tract of facial nerve.(D) CT scan. Left facial nerve's canal. (E) MRI. Evident facial nerves (arrows), not evident acoustic nerves on the both sides. The left internal auditory canal is hypoplastic, while the right is aplastic. Bilateral absence of the membranous labyrinth's signal. (F) CT scan. Remarkable hypoplasia of the left internal auditory. (G) MRI. Sagittal oblique scan: evident the intracisternal tract of the left facial nerve (arrow) [49].



Sensi A, Ceruti S, Trevisi P, Gualandi F, Busi M, Donati I, Neri M, Ferlini A, Martini A. LAMM syndrome with middle ear dysplasia associated with compound heterozygosity for FGF3 mutations. Am J Med Genet A. 2011;155A(5):1096-101.

Fig. 31 - LAMM syndrome (A) MRI scan. The image show facial nerves at the cisternal site (arrows); is not possible to see the normal signal hyperintensity of internal auditory canal and membranous labyrinth on the both sides. (B) CT scan. Bilaterally malleus' dysplasia (thick handle and irregular head). The facial canal is evident cranially to the middle ear (arrows); note the otic capsule substituted by a thin bony sheet and a remarkable hypoplasia and orizontalization of the ear drums. (C) CT scan. Bilateral aplasia of otic capsules. On the both sides is present staple (arrow) and absent oval window [49].

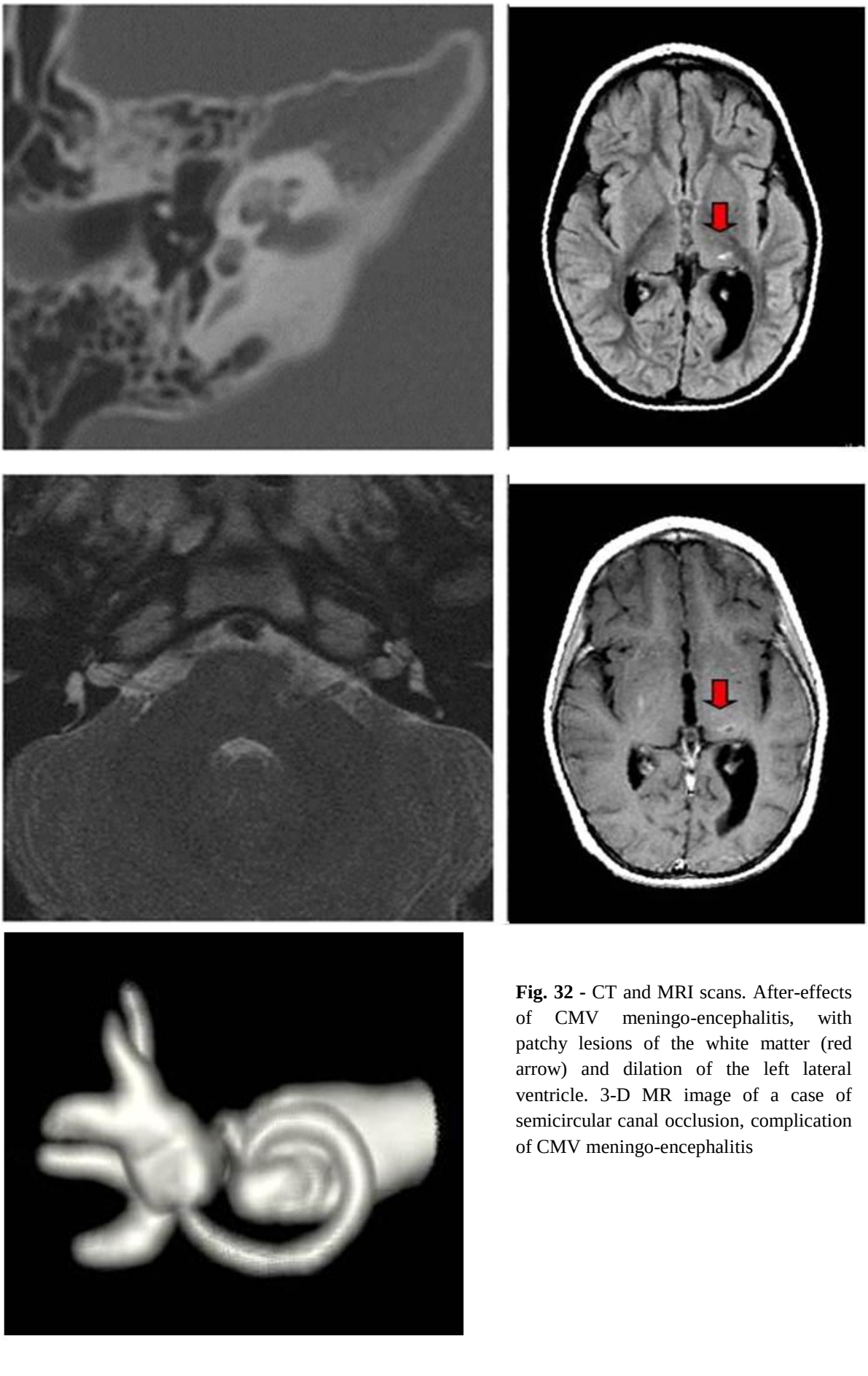


Fig. 32 - CT and MRI scans. After-effects of CMV meningo-encephalitis, with patchy lesions of the white matter (red arrow) and dilation of the left lateral ventricle. 3-D MR image of a case of semicircular canal occlusion, complication of CMV meningo-encephalitis

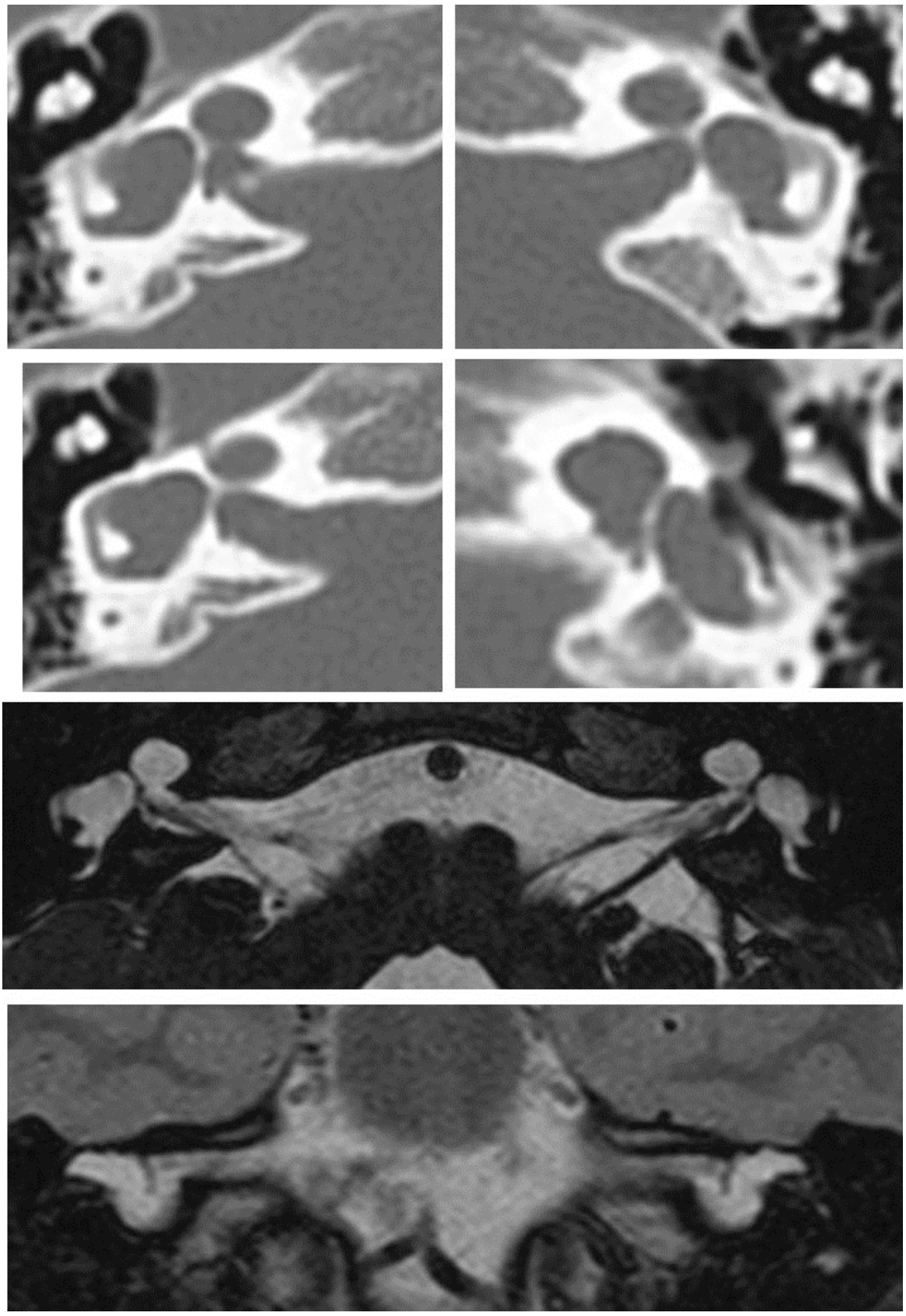


Fig. 33 A. – Cystic cochleae with apical turn aplasia, dilated vestibules, hypoplastic semicircular canals.

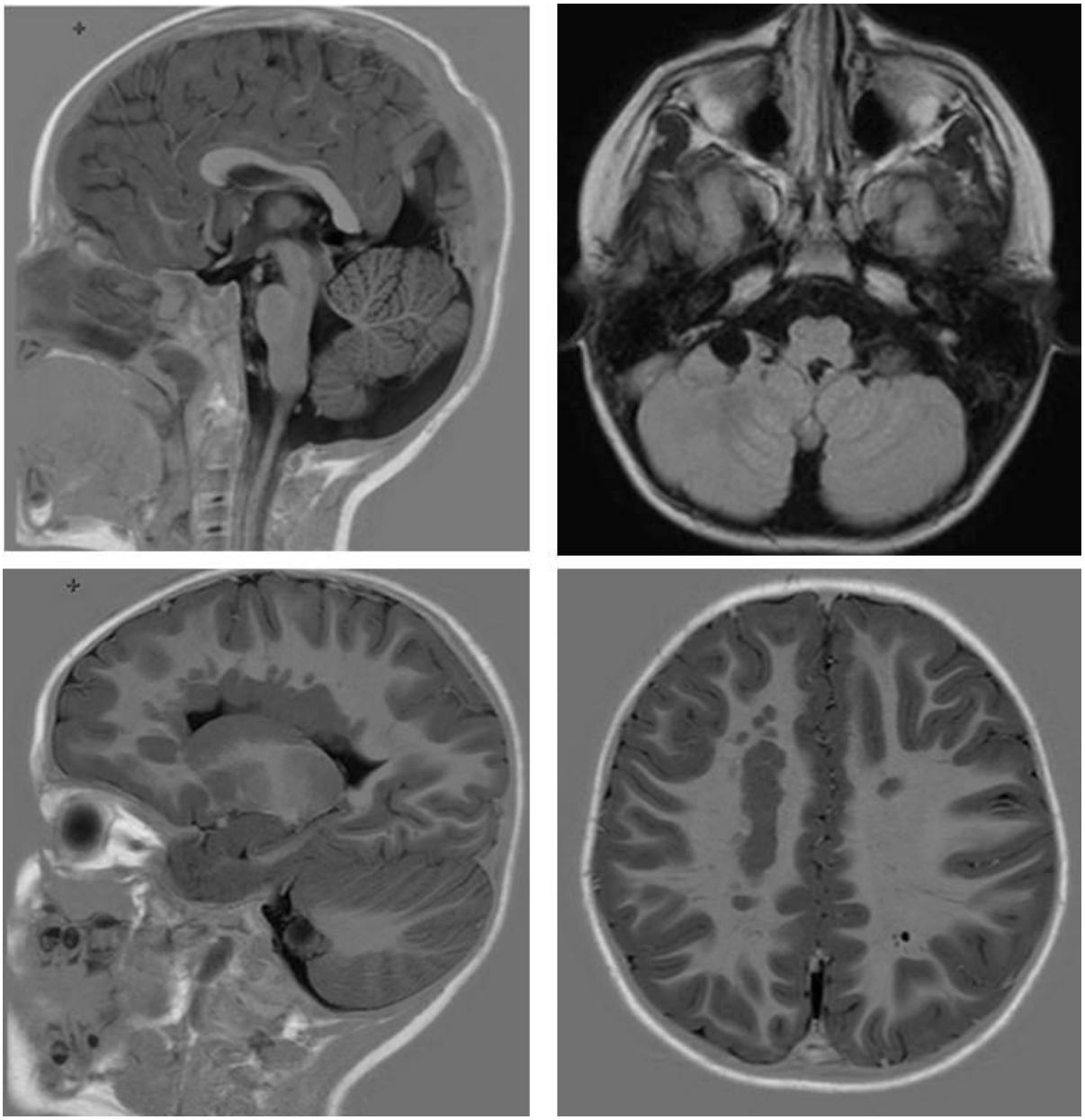


Fig. 33 B – MRI; dilated cisterna magna (or cerebellomedullary cistern); hypoplasia of the corpus callosum; dilated fourth ventricle; gray matter heterotopia; post-surgical anatomy of occipital myelomeningocele closure.

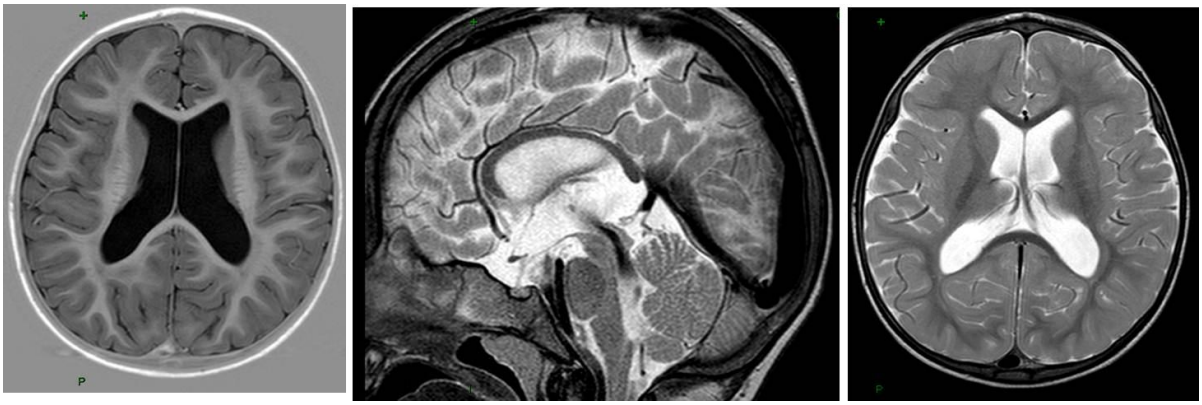


Fig. 34 MRI scans. hypoplasia of the corpus callosum; dilated lateral ventricles (external hydrocephalus

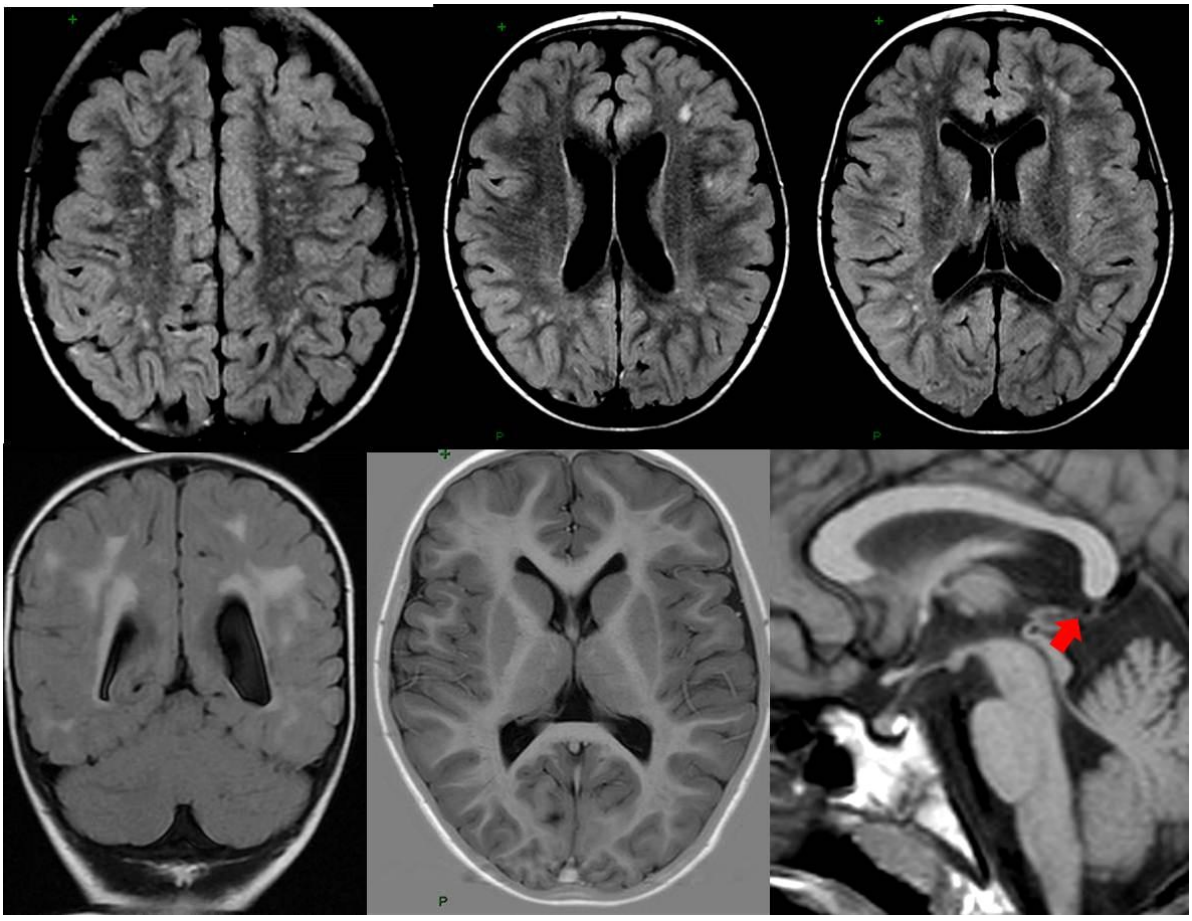


Fig. 35 MRI scans. CMV meningo-encephalitis, with patchy lesions of the white matter and dilation of the lateral ventricle; red arrow: pineal cyst.

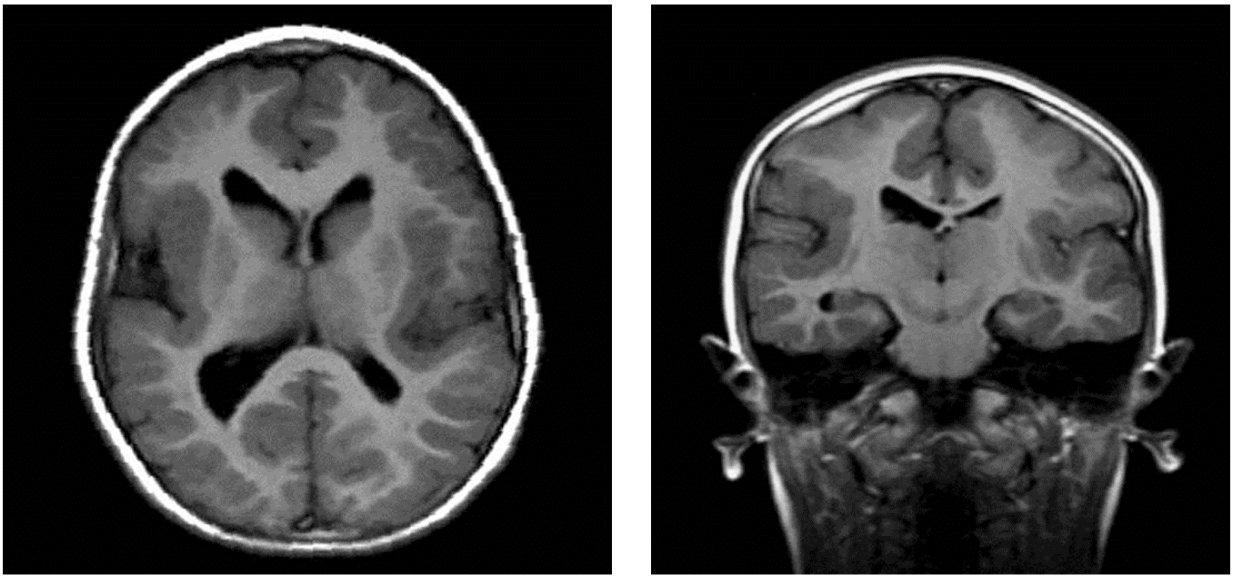


Fig. 36 – MRI scans. Cortical dysplasia.

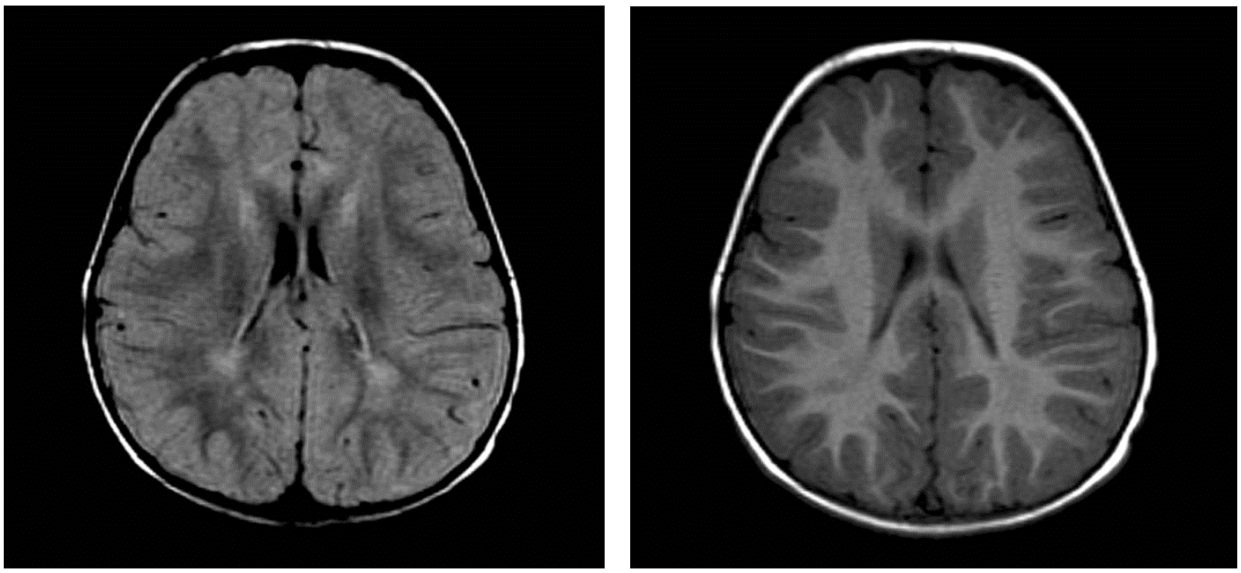


Fig. 37 - MRI scans. Parieto-occipital dysmyelinating areas, characterized by abnormal hyperintense signal on T2-FLAIR image in frontal and parieto-occipital periventricular regions

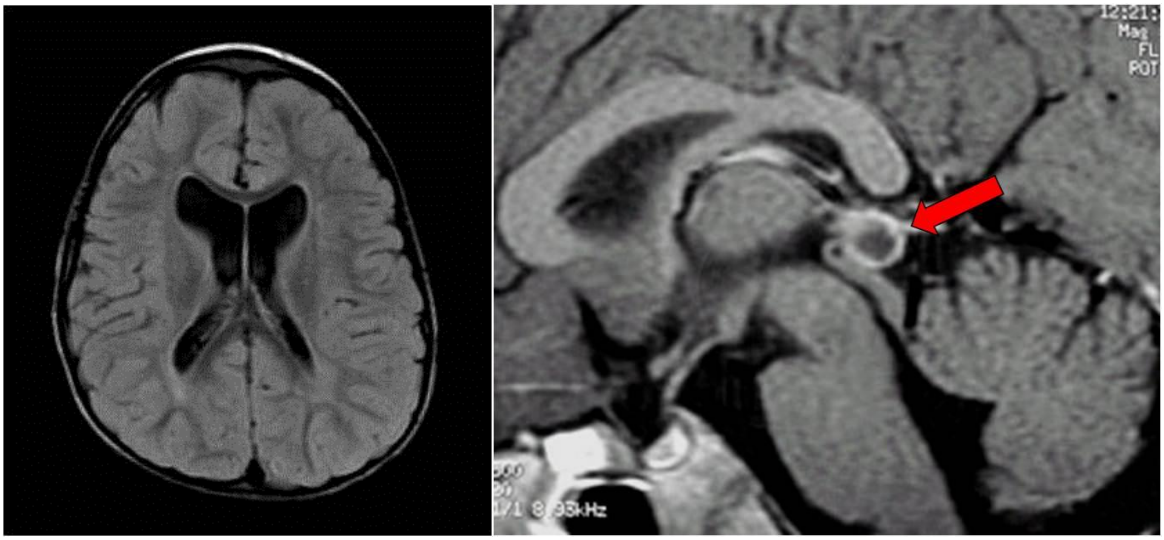


Fig. 38 MRI scans**.** This is an example of periventricular leukomalacia; you can see reduction of the periventricular white matter, abnormal hyperintense signal (on T2-FLAIR image) (of the white matter) in parieto-occipital periventricular regions and "ex vacuo" dilation of the frontal horns. Red arrow: pineal cyst.

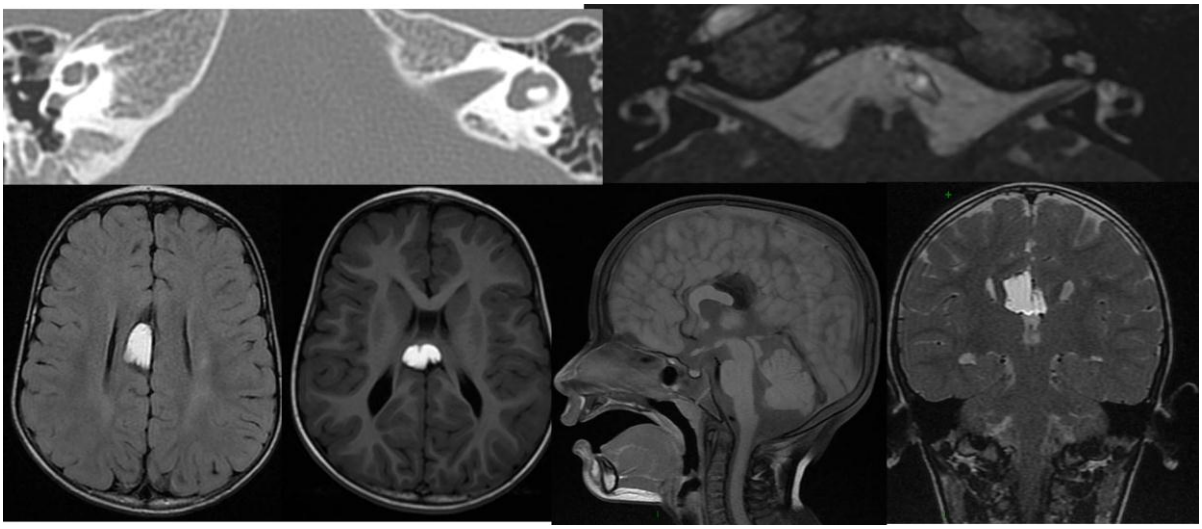


Fig. 39 - CT and MRI scans. Hypoplastic lateral semicircular canal; lypoma of the corpus callosum; agenesis of the posterior part and splenium of the corpus callosum; pellucid septum cyst; dilated cisterna magna (or cerebellomedullary cistern).

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