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Review

Case of Waardenburg Shah syndrome in a family with review of literature

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ABSTRACT

Waardenburg syndrome is a rare disease characterized by sensorineural deafness in association with pigmentary defects. Depending on additional symptoms, WS have been classified into four types. Waardenburg syndrome type 4, also called as Waardenburg Shah Syndrome is a very rare congenital disorder with astounding variable clinical expression, characterized by pigmentary abnormalities of the hair (A white forelock of hair, premature graying) and pigmentary changes of the iris such as heterochromia or homochromia irides, sensorineural deafness and Hirschsprung disease. Three genes have been bestowed so far in consociation with EDNRB, EDN3, and SOX10 genes. The pattern of inheritance is multifarious with the SOX10 mutation affiliation with autosomal dominant inheritance whereas the EDNRB and EDN3 genes are passed down in an autosomally recessive pattern.

Contents

1. Introduction

The syndrome was first described by Petrus Johannes Waardenburg in 1951 (Waardenburg, 1951) and the countenance as described includes lateral displacement of the medial canthi, Heterochromia iris, white forelock of hair and deaf mutism. In the antecedent 20 years, a myriad of studies (Arias, 1971; Hageman and Delleman, 1977) have apportioned Waardenburg syndrome (WS) into several forms, based on whether dystopia canthorum is present (type I) or absent (type II), and whether upper limb defects present (type III, Klein-Waardenburg syndrome) (Klein, 1983) or associated with Hirschsprung disease (type IV, Waardenburg Shah (1981). Waardenburg syndrome types I, II, and III demonstrate the autosomal dominant type of inheritance with an imperative complete penetrance and variable expression (Lalwani, 1996; Thorkilgaard, 1962). Dystopia canthorum which is defined as a

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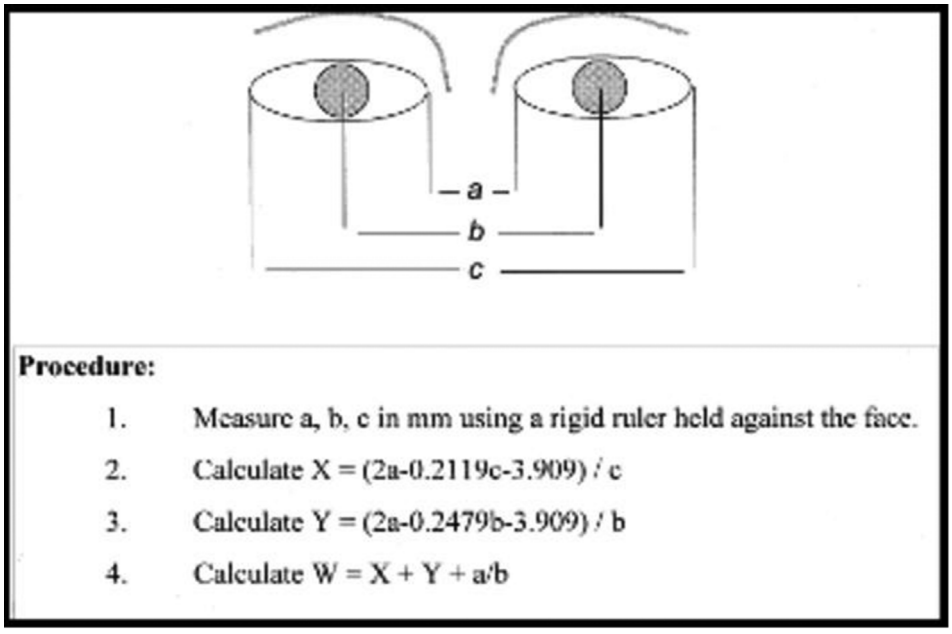

Fig. 1. Formula for measuring waardenburg index.

prominent broad nasal root with increased intercanthal distance is the most penetrated feature of WS and is found in 41.2%–99% of the reported cases (Choi et al., 2005). Arias and Mota (1978) in 1978 introduced a new putative Biometric index, Waardenburg index (WI) as a reliable measure of dystopia canthorum (Fig. 1). Heretofore, WI > 2.07 was heeded dystopic, but now WI > 1.95 is considered more pragmatic (Journal article from internet, 2018a). http://www.indianjotol.org/article.asp?issn=0971-7749;year=2012;volume=18;issue=4;spage=220;epage=222;aulast=Garg - ref7In 1992, the Waardenburg Syndrome Consortium proposed diagnostic criteria for Waardenburg syndrome, that included five major and five minor diagnostic criteria for Waardenburg syndrome (Farrer et al., 1992). Major criteria include sensorineural hearing loss, iris pigment abnormality (homochromia/heterochromia irides), hair hypopigmentation (white forelock or white hair at other sites on the body), dystopia canthorum (lateral displacement of inner canthi) and a first degree relative previously diagnosed with Waardenberg syndrome and, Minor criteria include skin hypopigmentation (congenital leukoderma/white skin patches), medial eyebrow flare (synophry), broad nasal root, hypoplasia alae nasi, and premature graying of the hair (before the age of 3 years). To be diagnosed as Waardenburg syndrome an individual must have two major criteria or one major plus two minor criteria (Journal article on the internet, 2018b) as explained in Table 1.

In 1981 Krishnakumar.N.Shah described WS type IV as an alternative of WS with involvement of white forelock of hair, pigment disorders and Hischprung disease (Shah et al., 1981). ***Type 4 is rare with only 50 cases proclaimed till 2016 with a* prevalence of <1/1000000** (Journal article on the internet, 2017). The affected children show such striking phenotypic features at presentation they are to be red flagged for their association with a yet to suffer intestinal aganglionosis. In the following case report, we chronicle the family of two children and a father with features of Waardenburg syndrome.

2. Case report

The propositus six years old, male child attended the ENT OPD at Mahatma Gandhi Memorial Hospital, Warangal, accompanied by his father. The male child had pre lingual hearing loss and mutism and his sister aged eight years who accompanied him, also presented with hard of hearing since childhood. The father of the proband was also examined for findings of waardenburg syndrome.

2.1. Case 1

The propositus, six years old boy, is the second child of a non-consanguineous marriage to healthy parents. The pregnancy and

Table 1
Major and Minor criteria of Waardenburg syndrome.

MAJOR CRITERIA	MINOR CRITERIA
Congenital sensorineural hearing loss With loss of >25 db for at least 2 frequencies, between 250 and 4000 Hz.	Congenital Leucoderma with several hypopigmented areas of skin (penetrance 30–36%)
Pigmentary disturbances of iris, complete heterochromia iris or segmental heterochromia iris, Hypoplastic blue iris (pentetrance 15–31%)	Medial eyebrow flare (synophrys)
White forelock of hair (penetrance 43–48%)	Broad nasal route (Penetrance 52–100%)
Dystopia Canthorum (penetrance 98%) *W > 1.95 is abnormal*	Alar Hypoplasia
Affected first degree relative	Premature graying of hair (penetrance 23–38%)

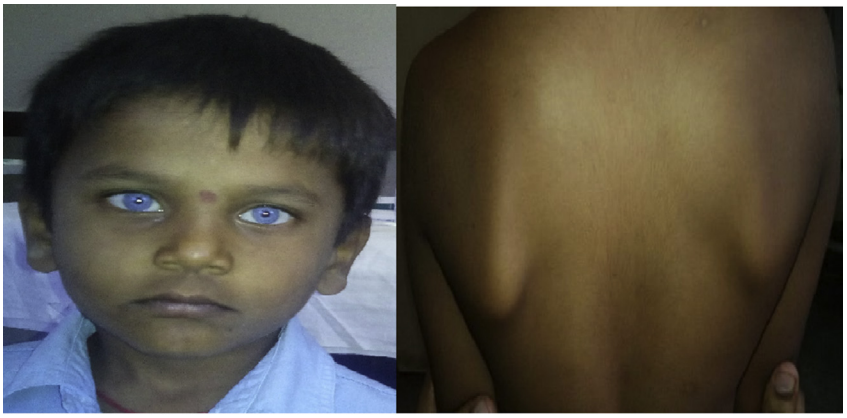

Fig. 2. Proband with homochromia irides (A) and *Sprengel deformity* with prominent medial border of scapula (B).

delivery were uneventful and the child passed meconium within 24 h of birth. However, at the age of 6 months he presented with distended abdomen and severe constipation and upon admission at the hospital an abdominal radiogram showed dilated bowel loops. Aganglionosis was suspected and he was treated with a colostomy and the rectal biopsy of the affected aganglionic segment divulged the absence of ganglion cells, supporting the diagnosis of Hirschsprung disease. The child was readmitted at age of one year and a definitive surgical repair to close the colostomy was performed. Thereafter he achieved normal motor and developmental milestones, and no neurological signs have been observed/reported by his parents till date. However, at the age of one and a half years his parents suspected hearing loss and an audiology examination was conducted and the tests revealed the following results: OAE: absent bilaterally; BERA: wave I to IV are absent bilaterally, and only wave V present. Again at age of six years the child accompanied by his father came to our hospital with the same complaint of unresolving vexed hearing loss affecting the very daily life of the child. Pure tone audiometry (PTA) wasn't possible when attempted as child didn't respond to the tones nor could he understand the procedure and so OAE, BERA and Computed Tomography of ear/mastoid were undertaken and the same results elucidated at childhood came back along with the CT of ear and mastoid portray a bilateral amorphous filling of middle ear. Facial examination demonstrated brilliant blue eyes (homochromia irides) (Fig. 2A) but neither pigmentary anomalies in the skin, nor a white forelock of hair, although a thorough history taken from the child's parents revealed that he had a transient white forelock of hair during infancy which disappeared spontaneously at around an age of year. ***Waardenburg index*** (WI) in our subject is 1.83 (a = 28 mm, b = 49 mm,

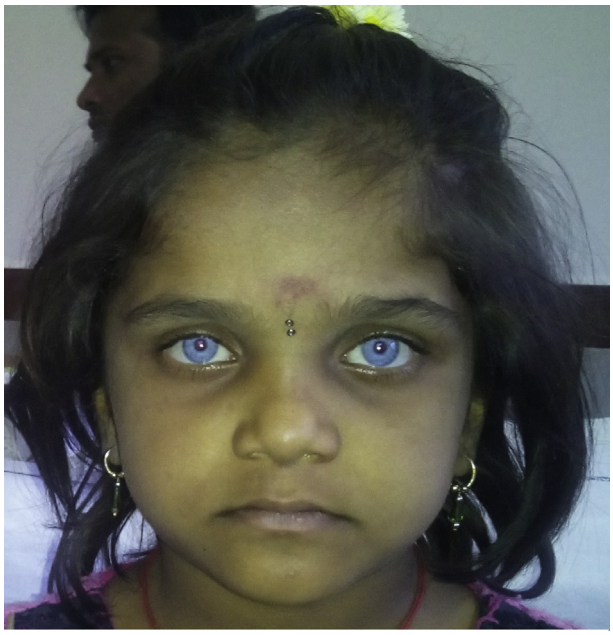

Fig. 3. Female sibling with broad nasal root and homochromia irides.

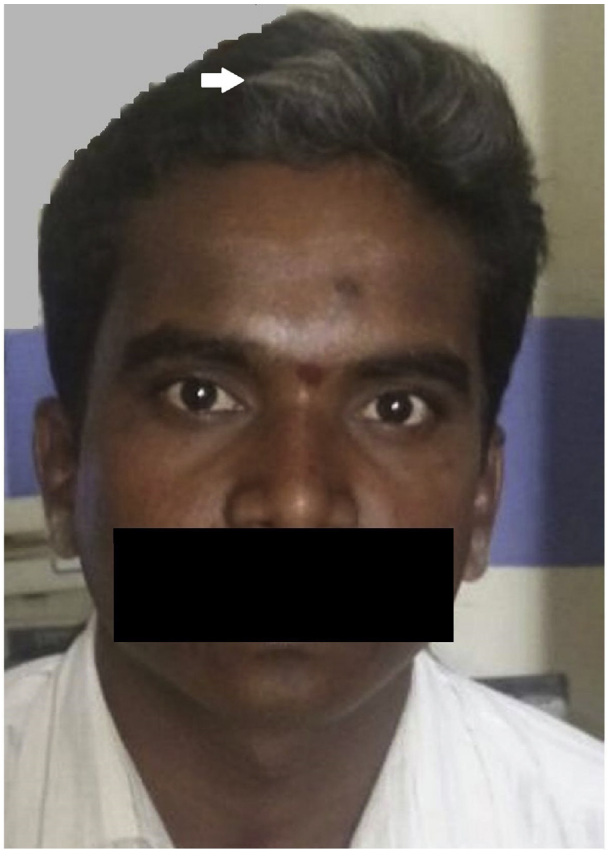

Fig. 4. Father of the siblings with white forelock of hair (white arrow).

c = 79 mm) ruling out Dystopia canthorum and the rest of facial examination was noted to reveal a broad nasal root, no synophrys,a prominent scapula medial border "*Sprengel deformity*" on his back (Fig. 2B). Visual acuity in both eyes was 6/6, pupils were round, regular and equally reacting to light and fundoscopy examination was normal. The male proband met features of 2 major criteria (Congenital sensorineural deafness, Homochromia irides) and 1 minor criteria (broad nasal root) along with history of Congenital Aganglionosis (Hischsprung disease) pointing out to unequivocal diagnosis of Waardenburg syndrome type IV.

2.2. Case 2

The sibling of the male proband aged eight years also suffered from hard of hearing since childhood and this was acknowledged at the age of 2 yrs whereupon no rehabilitation was taken up. She achieved normal motor and developmental milestones, and no neurological signs have been observed to date. At two years of age when she was suspected of hard of hearing and, consequential audiology tests revealed impoverished results, OAE: absent bilaterally; BERA: wave I to IV are absent with only wave V present bilaterally. The tests were repeated in our hospital during her visit, but the results were no different from those recorded earlier and PTA wasn't possible when attempted, as the child didn't respond to the tones and quite possibly didn't understand the procedure of the test. However, akin to her sibling, CT scan of ear/mastoids showed a bilateral amorphous filling of middle ear while the rest of the middle and inner ear structures were normal. Examination of the face showed extravagant bilateral brilliant blue iris (Homochromia irides), synophrys and a broad nasal bridge (Fig. 3) but there weren't any pigmentary abnormalities of skin or hair. ***Waardenburg index*** of 2.02 suggested presence of Dystopia canthorum (a = 33 mm, b = 54 mm, c = 86 mm). Opthalmology examination showed normal visual acuity, normal reacting pupils and a normal fundus. The female child met features of 3 major criteria (Dystopia canthorum, congenital senorineural deafness, and Homochromia irides) and 2 minor criteria (broad nasal root, synophrys) all combine to support Waardenburg syndrome.

2.3. Case 3

The father of the proband aged 35 years when examined revealed no history of hearing loss and no surgeries in the past. However examination of his face demonstrated the presence of Dystopia canthorum with a *W index* = 2.25 (a = 41 mm, b = 62 mm, c = 98 mm) and an idiosyncratic white forelock of hair persisting since childhood (Fig. 4). The father of the sibling met 2 major criteria (Dystopia canthorum, white forelock of hair) and 1 minor

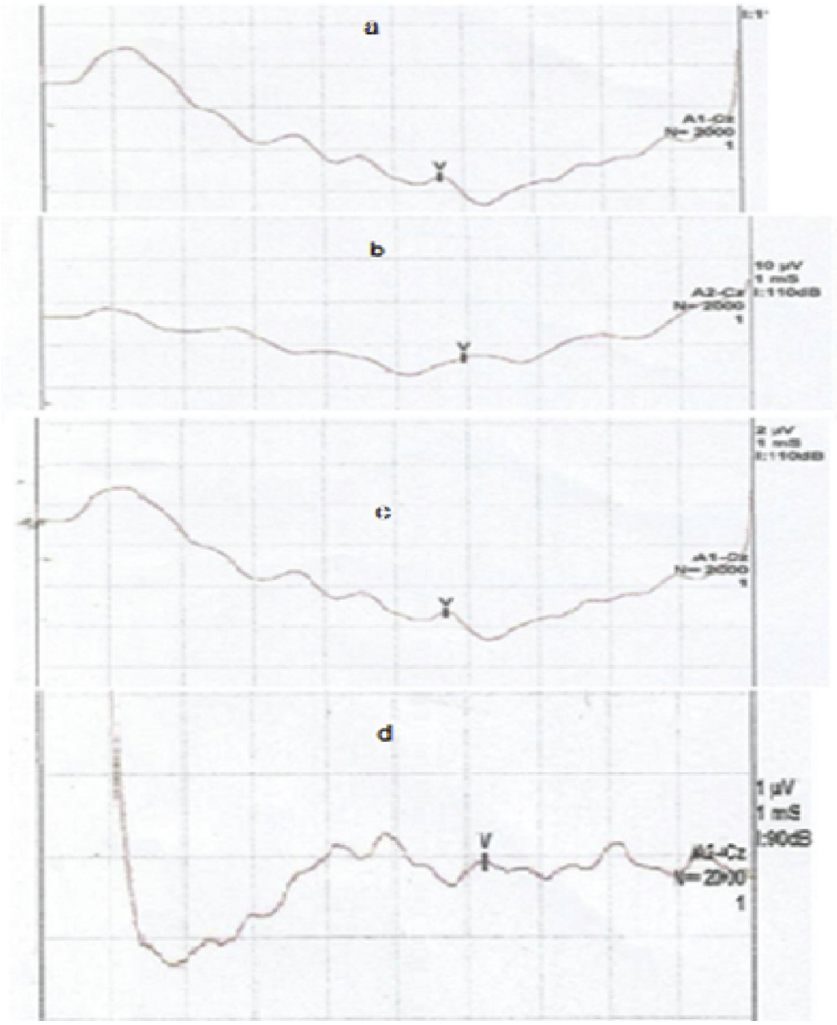

Fig. 5. BERA in proband (a,b) and female sibling (c,d) showing presence of only wave V at latency of 5.6 ms, 5.9 ms, 5.67 ms, 6.2 ms respectively.

criteria (broad nasal root) supporting diagnosis of Waardenburg syndrome.

3. Comments

3.1. Variability of clinical findings

The members in this family have exhibited very high levels of phenotypic variability, with a marked divergence of phenotypes within the family. The male proband having a history of aganglionosis, points in favor of WS4 with a possible mutation involving the SOX10 gene because of the gene's association with aganglinosis in many WS4 cases recorded so far. Both the siblings of the affected father demonstrate features of WS and so the possible explanation of transmission of the disease could be autosomal dominant with variable expression in the cluster of phenotypes.

3.2. Audiometric and radiology findings

The BERA shows bilateral normal latency in Wave V and absent Wave I-III in both the siblings (Fig. 5). The CT of temporal bones demonstrates bilateral amorphous filling of middle ear, in the proband and his sibling while the rest of the middle and inner ear structures, i.e. ossicles, semicircular canals, vestibule showed normal configuration (Fig. 6).

4. Discussion

Waardenburg syndrome type 4 which is also known as Waardenburg-Shah syndrome is a genetic condition that causes hearing loss, changes in colour of the hair, skin, and eyes and Hirschsprung disease (Journal article on the internet). **It is the rarest type among the four variants of WS with *a prevalence of* <1/1000000** (Journal article on the internet, 2017). As of 2016 the recorded number of cases worldwide comes to over 50 cases (Farrer et al., 1992) WS4 can be further subdivided into three categories videlicet, subtype 4A, 4B, 4C having mutations in the endothelin receptor type B gene (chromosome 13), endothelin 3 (chromosome 20) and SOX10 (chromosome 22) genes respectively (Read and Newton, 1997; Bondurand et al., 2007; Elmaleh-Berges et al., 2013; Journal article on the internet, 2014; Brown et al., 1993). The disease is usually inherited as either autosomal dominant fashion or autosomal recessive pattern. In postnal life SOX 10 is responsible for the functional maintenance of the enteric nervous system and is expressed in both neurons and glia of the enteric plexuses and in the nerves among the musculature in normal colon. In non-syndromic HD patients who do not have the SOX10 mutation, the SOX10 gene expressed in the sacral region may be involved in the pathogenesis of the abnormal nerve trunks through interaction with other factors (Sham et al., 2001a). Among the WS4 detected so far (i.e. 11 of 40 cases) with intestinal aganglionosis, all of them show a mutation associated with SOX 10 gene (Nadege et al., 2007; Borrego et al., ; Matthijs et al., 1999; Inoue et al., 1999; Touraine et al., 2000; Sham et al., 2001b). WS4 patients who have SOX10 mutations displayed different severity in the extent of intestinal aganglionosis suggesting be a correlation between the specific location of the mutation in the SOX10 sequence and the severity of intestinal aganglionosis (Pingault et al., 2010). An association between chromosome 13q and Hirschsprung disease has been reported previously, suggesting that gene on chromosome 13q is responsible for WS or HD or both (Van Camp et al., 1995). The varied phenotypic variation within the family members implies an incomplete penetrance of the genes although it would have been dominantly transmitted, with a marked disparity in aganglionosis with a female to male ratio of approximately 1:4 (Amiel and Lyonnet, 2001). Only a few familial WS4 cases have been described so far showing a high phenotypic variability (Pingault et al., 1998; Dang et al., 2011) speculating that mosaicism could very well participate in the incomplete penetrance of some features, while rest of the features being dominantly transmitted contributing to phenotypic variability in the context of these families (Southard-Smith et al., 1999). Skeletal anomalies such as Sprengel deformity (congenital upward scapular displacement) skull anomalies, bony defects of the thorax, abnormal upper limb length, syndactyly, and spina bifida have been noted (Waardenburg, 1951; De Saxe, 1984; De Saxe, 1984, 1984; Pantke and Cohen, 1971).

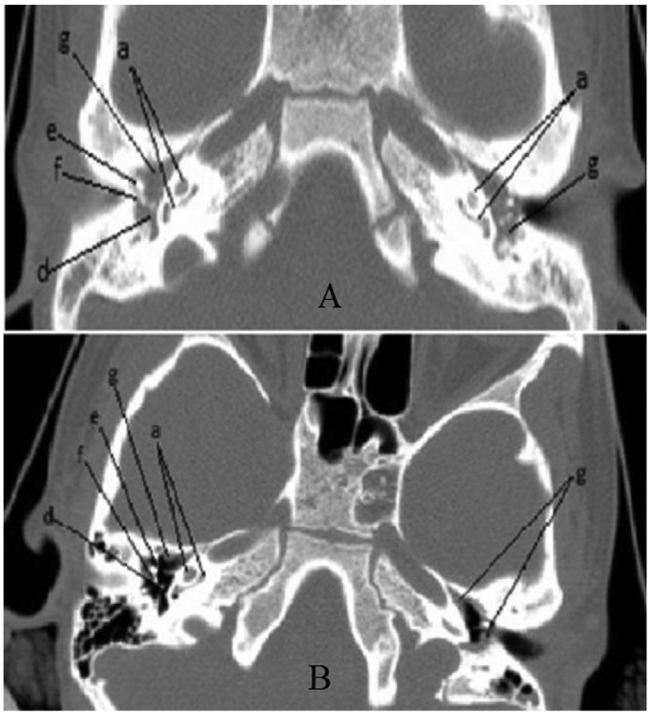

Fig. 6. CT of proband (A) showing bilateral filling of middle ear (g), cochlea (a), malleus (e), incus (f), stapes (d), CT of female sibling (B) with bilateral filling of middle ear (g), cochlea (a), malleus (e), incus (f), stapes (d).

5. Conclusion

In both the siblings reported in this paper with the diagnosis of WS4 the necessity for early diagnosis more importantly, paves the way for early and appropriate intervention. The spectrum and severity of symptoms and clinical findings associated with WS4 vary considerably among cases, even among affected members of the same family as discussed above; accordingly a careful medical history and clinical evaluation are required to differentiate among the different types of WS. Although the condition is rare, nonetheless its striking phenotypic features make WS a rare, but a highly recognizable syndrome. Because of the congenital hearing loss and other associated abnormalities WS4 is clinically important and, and an assiduous effort must be made in these subjects with the slightest suspicion of WS, so that an early intervention with either a cochlear implant or a hearing aid can ameliorate hearing. Evaluation of the disease helps the time ahead diagnosis of Hirschsprung disease, considering the higher morbidity and mortality in these babies so that early intervention essentially prevents the inevitable fulminant enterocolitis and sepsis. The siblings in the case have prelingual hearing losses and are considered poor candidates for

cochlear implants but nevertheless after a trial with hearing aid both the children are being planned on cochlear implants. Considering the above case, it goes without saying that every doctor and health personnel must understand that through examination is a must to abstain from undiagnosed disease, as in this case had the child been subjected to through history at time of surgery or at the time of birth an early intervention could have prevented hearing loss and above all a great amount of relief to the parents.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.joto.2018.05.005.

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