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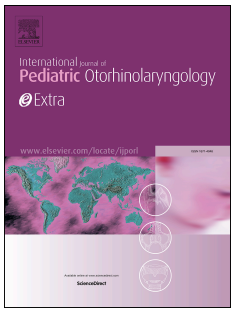

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DELAYED COCHLEAR IMPLANTATION IN POST-MENINGITIC DEAFNESS AND HEREDITARY COMPLEMENT C2 DEFICIENCY

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ABSTRACT

We report the case of an adolescent with post-verbal severe/profound sensorineural hearing loss, occurring as a consequence of two bouts of pneumococcal meningitis at 12 and 32 months of age. A possible immunodeficiency was investigated, revealing hereditary complement C2 deficiency (C2D). Given the insufficient benefit from high-power hearing aids, the boy received a cochlear implant (CI) at age 12. Despite the long interval of partial hearing deprivation and the post-meningitic etiology, improvement in open-set speech perception and quality of life were observed. The C2D did not favour post-operative infections nor meningitis recurrence. The risks and benefit of CI in this peculiar clinical circumstance are discussed after reviewing the literature.

Key-words: cochlear implantation, adolescence, complement deficiency, C2, immunological, meningitis.

1. INTRODUCTION

Lack of complement factors, such as hereditary C2 deficiency (C2D), affect the classical pathway of complement activation. It is associated with increased susceptibility to invasive infections by encapsulated bacteria, such as Streptococcus Pneumoniae and Haemophilus Influenzae type B. [1] In particular, the risk of meningitis with possible subsequent sensorineural hearing loss (SNHL) is increased. [2-8]

The CI itself has been also associated with an increased risk of pneumococcal meningitis, mainly in patients with inner ear malformations. [9] However, the CI may be the only means to recover the auditory function in post-meningitic patients with severe to profound sensorineural hearing loss (SNHL). The peri-operative infective risks in case of C2D should be carefully balanced in each patient against the speech perception benefits offered by the CI.

We report the case of a boy affected by C2D for whom the CI was initially contraindicated for the increased risk of recurrent meningitis, and who successfully underwent it without complications, many years after the diagnosis of hearing loss.

2. CASE REPORT

The patient was born in 1997 with normal hearing. The first episode of pneumococcal meningitis occurred at 12 months and lasted 15 days. One month later, bilateral severe SNHL was identified by behavioural audiometry, absence of otoacoustic emissions and stapedial reflexes, and electrophysiological tests (auditory brainstem responses with clicks and tone bursts). The baby showed an hearing threshold of about 80 dB HL. Better and more reliable behavioural responses were obtained from the right ear. High-power hearing aids (HA) were immediately supplied and verbo-acoustic training was started.

Speech perception outcomes with the hearing aids were sufficiently satisfactory. The behavioural pure-tone threshold average (PTA) reached 50 dB HL and the gain in free-field with HA was 32.5 dB HL; the boy slowly developed language skills, although not comparable to his age peer. At 24 months, the Production of Infant Scale Evaluation [10], the Meaningful use of speech scale [11] and the Infant-toddler Meaningful Auditory Integration Scales [12] scores were 100% and MacArthur Communicative Development Inventory [13] was at 75th percentile.

A second episode of pneumococcal meningo-encephalitis occurred at 32 months of age; a negative cerebrospinal fluid sample was obtained at an early stage of the disease (on the 5^{th} day from onset), after prompt intravenous antibiotic treatment. No further clinical neurological deficits due to menigitis were observed.

A search for possible risk factors for recurrent meningitis was then implemented. (Table I)

Having excluded other etiopathogenetic causes of recurrent meningitis, a diagnosis of C2D was finally established at 3 years of age, by performing a total haemolytic activity assay (CH50) that was greatly reduced: 125 U/ml, vs. normal serum values of 1000 ± 200 U/ml.

Genetic tests showed homozygosity for a deletion of 28 base pairs in the C2 gene, located on chromosome 6 at 6p21.3, responsible for the C2D type I. [14] Given the clinical characteristics of the disease, adequate prophylaxes and vaccinations were performed.

Further audiological evaluation (on February 2000) showed a worsening of the bilateral severe

SNHL, especially in the left ear; and the positive effects of the rehabilitation with HA started to weaken. Tympanograms were type A bilaterally, stapedial reflexes and otoacoustic emissions were absent. Auditory brainstem responses (ABR) could not be elicited at the highest levels of stimulation. The behavioural PTA at low and middle frequencies in free-field with HA was no better than 80 dB HL; the toddler did not react to loud sounds of higher frequencies. Word recognition scores with age-appropriate material in a closed set (pictorial aid) at signal to noise (SNR) +10 dB dropped to 25%.

A CI was offered at 3 years of age, but both the parents and the Surgeon were concerned about the risk of a new episode of meningitis. The parents asked for another consultation, where both the other Surgeon and Anesthesiologists denied the CI, based on a supposed increased peri-operative infectious complication risk. From an immunological viewpoint, the risk of meningitis after CI was considered too unpredictable on repeated visits at the age of 5 and 7 years at different institutions. HA use and oral rehabilitation were continued but, for the next 5 years, the family discontinued any medical control since they felt discouraged and hopeless.

When the boy was 12 years old, he was again referred to our institution by his Family Paediatrician for an audiological evaluation because his relational and communicative performances were inadequate for his age and the parents reported a worsening of school performances: he was unable to follow the lessons unless the teachers were facing him o writing; the performance scores on many topics (mathematics, physics, Italian and English language, history and geography), were insufficient. A severe lack of oral language production and multiple phonetic difficulties were assessed. He tended to discontinue the use of his hearing aids during the day, owing to subjective insufficient benefit. Actually his audiogram showed hearing residuals on the low frequencies. (Figure 1) The speech understanding and communication difficulties progressively isolated him from his peers. The child appeared emotionally fragile, switching from a depressive mood; his social participation was almost null. The outcomes of the audiological workup were unchanged: the boy's speech perception abilities were null without lip-reading; only by visual aid he was able to

correctly identify 58% of vowel-consonant-vowel and to recognize 41% of bisyllabic words and 80% of short sentences in an open set. (Table II) We believe that the reported difficulties were attributable to the more demanding listening environment of the middle school.

High-resolution computed tomography and magnetic resonance imaging excluded central nervous system pathologies and assessed a normal patency of the cochlear lumen. Neuropsychological examination did not reveal neurological lesions or disorders concerning intelligence and cognitive abilities, in spite of having suffered from meningitis. [15]

~~Both parents and the boy were realistically aware of the limited expectations with a late CI and a post-meningitic etiology of~~ deafness; nevertheless, After repeated counselling, ~~they~~ both parents and the boy showed a strong motivation, normal psychosocial attitude and a positive familial relationship and reciprocal support. All family members, including the boy himself, signed a specifically designed informed consent to the operation.

At the light of new relevant knowledge about C2D [16, 17] and after a new multidisciplinary evaluation, CI was considered feasible, provided that the IgG and IgG subclass levels were normal and that protective levels of antibodies against Pneumococci, Haemophilus Influentiae and Meningococci were achieved by re-vaccination, that was immediately accomplished.

On November 2011, an MXM Digisonic SP cochlear implant was inserted in the left ear. Prophylaxis with a daily dose of 2 g Ceftriaxone was administered immediately before and after surgery, and continued for 10 days. No cochlear ossification or fibrous obstruction were observed during the surgical procedure, which did not present any complication; a full insertion of the electrode array into the scala tympani was achieved. The postoperative course was uneventful, and the patient was discharged in good health 2 days after surgery. At the first postoperative control, 4 weeks after surgery, the wound had healed well, and no signs of flap infection or necrosis were present. To date, after a follow-up of 5 years, no local or systemic complications have occurred.

Post-operative speech tests results at 12, 18, 24 and 48 months are reported in Table II and compared to the pre-operative scores.

All tests were initially performed in quiet, in a sound booth, with and without lip-reading, and then repeated with a masking noise [cocktail party] at a signal-to-noise ratio [SNR] of +10 dB HL. The hearing aid in the right ear was removed during testing.

Although the benefits seemed limited during the first year after the implantation (Table II) in the long run the kid's speech perception skills started improving: at 18 months he was able to identify without the visual support 90% of the words in a closed set, whereas only 20% of the words and 10% of sentences in an open set. He still experienced great difficulties in a noisy environment, but his lip-reading aptitudes helped him a lot: in an open set he could correctly repeat 90% of the words and 100% of the sentences by watching the speaker.

The performances steadily increased thereafter: at 2 years post-operatively the WRS and SRS without lip-reading reached 40% and 20%, respectively (while in noise they were still close to zero); with the help of lip-reading he scored better than 90% in all tasks, except in the presence of a masking noise.

Four years after surgery he had achieved a further significant improvement: without lip-reading he could identify 42% of VCV and 100% of words in a closed set; in an open set he was able to correctly state 60% of words and 22% of sentences. With the support of lip-reading he reached a score of 100% in all tasks. The perfomances still dropped when a masking noise was added.

The CI data logging system currently indicates that the boy is using his implant for an average of 11 hours and 42 minutes per day; thus, he can be considered a "good user" [18] and has drastically enriched his quality of life: he reported a subjective benefit of 8 in a 10-points visual analogue scale [VAS], compared to a score of 1 in the pre-operative assessment.

Spatial and Qualities scale (SSQ) [19] used for subjective evaluation of hearing score increased to 376 with CI (compared to the previous score of 167 with hearing aids), 48 months after activation with the best improvement in the speech scale.

3. DISCUSSION

C2D is a rare and often underdiagnosed condition among primary immunodeficiencies: its estimated prevalence is 1:20,000 in Caucasians. [20]

Two main variants of C2D have been distinguished: C2D *type I* is characterized by the absence of detectable C2 synthesis; C2D *type II* is caused by a selective block of C2 secretion. [21]

Some patients with C2D type I or II remain asymptomatic, but it is estimated that 40% develop autoimmune disease and 50% develop recurrent infections, predominantly caused by encapsulated bacteria (Streptococcus Pneumoniae, Haemophilus Influentiae and Neisseria Meningitidis). These infections have a tendency to produce severe complications like meningitis or septicaemia in a significant proportion of C2D patients. [3] Patients with C2D who submitted to general surgical procedures showed post-operative complications, such as septicaemia or site infections. [22] On the other hand, the rejection rate of the implantation of devices or alloplastic materials in C2D is reported to be equal to normal subjects. [23-26] As far as we know, up to date there are no reports on the outcomes or post-operative complications of cochlear implants in C2D patients.

A complement deficiency might hinder the body's ability to counteract a possible post-operative infection, despite adequate antibiotic covering. The consequences would be catastrophic: not only the implant should be removed but the infection could spread to adjacent soft tissues and even to distant sites, leading to a dreadful generalized septic syndrome, which could endanger the patient's own life. Most Surgeons and Anesthesiologist would therefore be reluctant to perform a non-life-saving procedure, as it happened with our young candidate to a CI.

When exploring the risk of CI complications in other immunodeficiency diseases, only cases of HIV seropositivity are reported to benefit from CI without increased surgical risk. [27] and a case of x-linked agammaglobulinemia who failed the CI, since the occurrence of post-operative repeated infectious complications nonetheless the immunoglobulin replacement treatment conducted to the decision of explanting the CI. [28] Since the infections reported in persons with with hypo- or dysgammaglobulinemias include those with encapsulated bacteria and has a similar spectrum of

infections seen in a complete deficiencies of the components of the classical pathway (C1q/r/s, C4, and C2), there were no evidence in the literature supporting the choice of performing a CI.

In agreement with other C2D studies, [16] a multidisciplinary evaluation of the risks related with CI surgery was mandatory for our young patient with C2D; the procedure was finally considered feasible and safe, considering that the IgG and IgG subclasses levels were within normal limits and the serum antibodies against Pneumococci, Hemophilus influenzae and Meningococci were adequate. As a preventive measure, revaccination to Pneumococcus and to Meningococcus was achieved, in agreement with Jönsson et al (2012). [17]

Additional perplexities on the indication to the CI in the reported boy derived from his clinical history: the post-meningitic nature of deafness and the long period of partial hearing deprivation (9 years).

The first issue was the feasibility of the CI and its expected outcomes: ~~even if the imaging assessed a patent cochlear lumen,~~ our personal experience with post-meningitic CI was not too encouraging: in 2 out of other 11 operated children [unpublished material] the insertion of the array was incomplete; even after full insertion the speech perception abilities did not exceed an average 65% WRS at 1 year post-implantation; in all cases except one the post-meningitic CI recipients never equalled their peers with other etiologies of deafness, even in the long term follow-up. This is a well-known phenomenon, related with the reduced survival rate of spiral ganglion cells in post-meningitic cochleas. [28-30] The personal experience with CIs after long-term deprivation was also quite disappointing: in agreement with the literature [31-33], none of our pre-verbal children receiving a CI after 10 years of age ever equalled the speech perception performances of earlier CI recipients (below 3 years of age at surgery).

Against the odds, our patient significantly benefited from the CI: the words identification in a closed set improved from null with the HA to 90% with the CI at 24 months after its activation; the words recognition score in an open set grew from 0 to 40% in quiet.

After 4 years he exploited better his good lip-reading ability, but he still experienced difficulty in understanding speech in a noisy environment. Subjective scoring of hearing disability decreased significantly with ongoing CI use.

Despite the CI outcomes in our young patient remain lower than those of peers implanted at an earlier age, his overall quality of life was greatly enhanced by the CI, including school learning, emotional stabilization and socialization.

No complications ensued following surgery and the young boy is regularly using his device in an efficient and rewarding manner at more than 4 years after implantation.

After multiple conflicting otological consultations warning about the surgical risks, that delayed the decision, the Pediatrician's advice was crucial in inciting a cost-benefit evaluation of the CI long after the "sensitive period" for language acquisition (0-3 years of age).

4. CONCLUSIONS

Provided the necessary precautions are taken in each single case, i.e. full immunological assessment, re-vaccination against Pneumococci, Haemophilus I. and Meningococci, and prolonged post-operative antibiotic prophylaxis, patients with increased infectious risk owing to C2D need not be excluded from CI with its undisputable benefits. The reluctance to undergo surgery is frequently due to inadequate information regarding the entity of the risks.

The positive outcome of this case suggests that a CI should not be denied to any C2D patient per se, but adequate counselling should be provided, and risk analysis should be performed by multidisciplinay approach in a timely manner in order to avoid undesired delays.

Furthermore, this case highlights the role of paediatricians in the parents' counselling providing effective information about the disease.

Table I. Results from basal serum immunological analyses at 3 years of age.

	Value	Normal range
Total IgG (mg/dL)	934	462-1710
IgG1 (mg/dL)	714	310-1050
IgG2 (mg/dL)	67	41-245
IgG3 (mg/dL)	26	9-69
IgA (mg/dL)	71	27-173
IgM (mg/dL)	161	62-257
Lymphocytes, CD3+ (%)	71	56-86
Lymphocytes, CD4+ (%)	54	32- 64
Lymphocytes, CD8+ (%)	20	13 - 37

Table II. Results from speech test before and after CI.

			Post-implantation			
		Pre- CI	1 year	18 months	2 years	4 years
without lip-reading	VCV	0%	18%	28%	42%	42%
	WIS	0%	60%	90%	100%	100%
	WIS in noise [SNR +10]	0%	40%	50%	75%	80%
	WRS	0%	0%	20%	40%	60%
	WRS in noise [SNR +10]	0%	0%	0%	0%	40%
	SRS	0%	6%	10%	22%	22%
	SRS in noise [SNR +10]	0%	2%	6%	6%	6%
With lip-reading	VCV	58%	63%	65%	70%	100%
	WIS	45%	90%	100%	100%	100%
	WIS in noise [SNR +10]	0%	60%	70%	90%	100%
	WRS	41%	82%	90%	100%	100%
	WRS in noise [SNR +10]	0%	0%	25%	45%	60%
	SRS	60%	100%	100%	100%	100%
	SRS in noise [SNR +10]	0%	20%	55%	60%	85%

VCV - Vowel-consonant- vowel identification (in closed-set), in quiet

WIS - Bisyllabic words identification scores (in closed-set), in quiet

WRS - Bisyllabic words recognition scores (in open-set), in quiet

SRS - Recognition scores for short sentences (in open-set), in quiet

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CONSENT

Written informed consent was obtained from the patient and the parents for publication of this case report and any accompanying tables. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

LIST OF ABBREVIATIONS

C2D - hereditary C2 deficiency**;** CI - cochlear implant; HA – hearing aids; SNHL - sensorineural hearing loss; csf – cerebro-spinal fluid, .

COMPETING INTEREST

The authors declare no competing interest, financial or not.

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AUTHOR'S CONTRIBUTIONS

FDB has followed directly this case report and wrote the article
LT supported the decision of proposing CI in the risk analysis, due to his exerpertice on C2D.
DZ wrote, supervised and reviewed the article.

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