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ORIGINAL ARTICLE

Paediatric cochlear implantation in the critical period of the auditory pathway, our experience

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Abstract
Introduction: Numerous experimental and clinical studies have suggested a critical or sensitive period in which the auditory pathway develops its greatest potential in terms of plasticity and learning. Early cochlear implantation performed in prelingual deaf children in this period provides a better prognosis for language acquisition. The aim of this study is to show the importance of cochlear implantation before this critical period ends.
Methods: We conducted an observational, longitudinal, retrospective study of 57 children suffering profound prelingual bilateral sensorineural hearing loss who had received Advanced Bionics implants at our ENT department between June 1998, and November 2006. Data on their audiometric thresholds, the disyllabic word test adapted to children, open-set sentences recognition test and the Nottingham scale were analyzed.
Results: The analysis of audiometric thresholds showed no differences between children receiving the implants at different ages. However, statistically significant differences ($P<.05$) were found in speech tests between groups of children receiving the implants before and after 4 years of age.
Conclusions: Our results are in line with other publications showing differences in auditory performance when comparing children with early implants versus children receiving the implants at a later age. We found the greatest differences at 4 years of age. Nevertheless, these findings should not exclude children over this age from implantation.

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PALABRAS CLAVE
Plasticidad cerebral;
Implantación precoz;
Periodo crítico;
Periodo sensible;
Resultados de implante coclear

La implantación coclear pediátrica en el periodo crítico de la vía auditiva, nuestra experiencia

Resumen
Introducción: Datos experimentales y clínicos apuntan a que existe un periodo crítico o sensible en el que la vía auditiva desarrolla el mayor potencial de plasticidad y aprendizaje. Se ha demostrado que la implantación coclear precoz en ese periodo conlleva un mejor pronóstico respecto a la adquisición del lenguaje. El objetivo del presente trabajo es demostrar la importancia de la implantación coclear en ese periodo crítico.
Métodos: Se ha realizado un estudio observacional, longitudinal y retrospectivo en 57 niños con hipoacusia neurosensorial bilateral profunda de inicio prelingual implantados en nuestro servicio, entre junio de 1998 y noviembre de 2006, con dispositivos de Advanced Bionics. Se han analizado los resultados obtenidos en audiometría tonal liminar, test de bisílabos adaptado a niños, test de frases en abierto y escala de Nottingham.
Resultados: No se han observado diferencias en el análisis de los umbrales audiométricos de los niños implantados a distintas edades. Sin embargo, cuando se analizan los resultados de los tests logoaudiométricos, sí se han encontrado diferencias estadísticamente significativas ($p<0,05$) en los grupos de niños implantados antes y después de los 4 años de edad.
Conclusiones: Nuestros resultados son coherentes con los de otras publicaciones en las que se evidencian claras diferencias en el rendimiento auditivo de los niños implantados precozmente con respecto a la implantación más tardía. Hemos encontrado las mayores diferencias en el límite de los 4 años de edad. No obstante, estos hallazgos no deben hacer que se excluya de la implantación a los niños que hayan sobrepasado esa edad.

Introduction

Varied evidence confirms that there is what we call a critical period of the auditory pathway, in which biochemical and morphological events are produced which mark the fate of listening comprehension. The brain is in constant change; at birth it is partially myelinated and diffusely interconnected, then it matures and becomes a complex organ tuned to relate to the conditions of its environmental niche. Through memory and learning, thanks to synaptic plasticity, the mature brain adapts to the changing contingencies of its environment by selecting the most relevant stimuli.

The cerebral cortical plasticity is based on basic principles which were presented by Thomas Elbert[1]:

- Disuse or deafferentation (after injury) lead to the invasion of the cortical areas which are not used by neurons in neighbouring areas.
- Increased use causes the expansion of the cortical representation.
- Synchronous stimuli involve the fusion of cortical zones representing those stimuli.
- Asynchronous stimuli induce the segregation of cortical areas representing these stimuli.

These principles would involve, in the case of congenital auditory deprivation, a neuronal development such that the brain areas initially intended for auditory processing would be used to process other sensory input. This happens when no auditory input is established during the critical period in which these processes occur, the study of which has been confirmed from various points of view. In fact, a study conducted by Jung et al[2] in the inferior colliculus of rats in different stages of development shows that, after birth, the expression of GAP-43, a protein involved in axonal growth and synaptogenesis, and other proteins decreases during foetal development. This shows that, while neurons gradually assume their specific function, there is a decrease in the molecular complexity and concentration of proteins that mediate neural development. Other studies conducted by Ahn[3] show that ablation of both cochleae in rats leads to, in the weeks following, a decrease of metabolism in cortical areas related to hearing, demonstrated by positron emission tomography with fluorodeoxyglucose after injection of 2-deoxyglucose. However, after several weeks, metabolism was reactivated, allegedly due to the invasion of these not used cortical areas by neurons in nearby areas, which has been termed cross-modal plasticity.[4-7]

In addition electrophysiological studies have shown the development of the auditory pathway and the impact on it of hearing deprivation. Using cortical potentials in cats with normal hearing and congenitally deaf, Kral et al[8] have found that the functional development of the auditory cortex critically depends on the listening experience, so that in cases of auditory deprivation the development of waves is delayed and they have responses with a smaller amplitude. From the fourth month of life, animals with congenital deafness present a reduction in the activated areas and lower synaptic currents than those in the control group. However, cats with normal hearing at this age have the same patterns as adult cats. Studies conducted by Nagase et al[9] have shown that rats with a drug-induced hearing loss after birth showed a greater expression of Fos than control rats with normal hearing in the contralateral inferior colliculus following electrical stimulation of a cochlea. These findings also indicate that changes take place in the auditory processing as a consequence of neonatal hearing loss.

Besides these and other findings observed in laboratory through electrophysiological and cytochemical techniques, the increasingly wide use of cochlear implants has become an essential tool to obtain a greater understanding of neuronal plasticity in humans. The process of cochlear implantation involves the replacement of a sensory system that can take place at different stages of brain development because the age of implantation varies depending on the circumstances of each case.

In implanted children it has been possible to demonstrate by brainstem auditory evoked potentials (BAEP), a decrease in the latency of wave V as well as an increase in amplitude of waves I and III with increasing exposure time to stimulation through the cochlear implantation.[10] That is, the same pattern of development of the BAEP in children with normal hearing is reflected in newly implanted children after the first months of stimulation.

The analysis carried out on the evolution of language in relation to age of implantation and comparisons with children with normal hearing show that, the earlier the implantation takes place, the closer the results are to those obtained in children with normal hearing.[11] However, further on implanted children evolve to lower levels and it is even possible that they may never reach the levels of children with normal hearing. Thus, it has shown a "critical" or "sensitive" period for the development of language. Cochlear implantation after this critical period is related to a gradual decline in the ability to acquire and develop language. These evidences have also been observed by electrophysiological observations. Thus, from the study of the electrical activity of the auditory cortex in subjects with cochlear implants and their comparison with those of children who were implanted at different ages, evidence is shown that children who receive cochlear implants before 42 months of life have a latency of the P1 wave close to that of the population with normal hearing.[12] Therefore, one may consider hearing deprivation as a major obstacle to the acquisition of language[13]; in addition, the early restoration of hearing through cochlear implant is a key factor in forecasting language acquisition.[14]

Through this work, we aim to demonstrate the importance of implantation age during the critical period of development of the auditory pathway, from the analysis of the results of children who received a cochlear implant at our centre. We also seek to establish the clinical threshold for this critical period of plasticity of the auditory pathway.

Methods

We have performed a retrospective and longitudinal observational study in 57 children with profound or severe bilateral sensorineural hearing loss of grade II with prelingual onset (acquired before 2 years of life) with cochlear implants. All these children were implanted in our department between June 1998 and November 2006 with devices from Advanced Bionics LLC, with different generations of the device according to the date of implementation: C-I, C-II, and HiRes90K. All subjects were operated on by the same surgeon, the programming methodology applied was the same in all cases and the follow-up speech therapy recommendations were identical in all cases. Individuals with other concomitant conditions to the hearing loss were not included in the study, so as to homogenize the sample and discard factors of bias. All children in the series underwent language assessments periodically according to the protocol designed at our centre. In this study we have analyzed the evaluations during the first 5 years of follow-up, except in children implanted later, for whom there was a shorter time of evolution. However, for all subjects included there are results for at least the first 2 years after implantation. We analyzed the results obtained in the following audiological tests: liminal tonal audiometry, disyllabic test adapted to children,[15] open phrase test,[16] and Nottingham scale.[17]

To achieve the objectives of this study, the sample was divided into 4 groups according to the age of each child at the time of implantation. Thus, the children were grouped into group I (children implanted at age 2), group II (children implanted between ages 2 and 3), group III (children implanted between ages 3 and 4), and group IV (children implanted at ages over 4 years).

This aimed to explicitly show the differences in performance that might exist between children implanted within the critical period of brain plasticity which, as other authors have defined, is in the first 4 years of life. To make clear the possible differences that could appear the Student t test was systematically applied between different pairs of age groups and the threshold of statistical significance was established at $P<.05$.

Results

The age distribution of our sample is shown in Table 1. The average age of implantation was 4.56 (4.39) years (range, 12 months-13 years; mode, 2 years).

The analysis of the audiometric thresholds obtained in open field using the hearing aid before implantation, and with the cochlear implant after it, in the different groups of children and at different stages of evolution, shows that at 3 months the implanted patients achieved stable audiometries at around 30 dB SPL. The Student *t* test to compare the audiometric thresholds of the different groups showed no statistically significant differences between them. Table 2 presents the results of these comparisons, all of them $P<.05$, significance threshold established in this work. Figure 1 shows the averages and ranges for 2 standard deviations of the different groups during the first year after implantation.

The analysis of evaluations by the 2-syllable word test adapted for children shows that children implanted before age 4 (groups I, II, and III) offer better and earlier results, with scores between 80% and 100 % (Figure 2). However, children implanted at ages over 4 years (group IV) show a roof in their evolution which they do not overcome despite the passage of time and the average value is close to 40 % Table 2 presents the statistical significance of comparisons among the groups in each of the periods. There are statistically significant differences between groups III and IV for the entire period under review and, occasionally, in the assessment carried out after 2 years between groups

II and IV. However, there are no differences between the other groups.

The results of the test of phrases without lip-reading show a rapid evolution of groups I and III, which reach 80% 100% from the second year after implantation. This is not the case, however, for group II and even less for group IV. It is important to add that out of the 6 subjects in group II, only 3 of them have available monitoring data from the third year, so the confidence interval is very wide in these cases (Figure 3). The comparison of the results by groups yields a statistically significant difference between groups III and IV for the first 4 years of evolution and also

Table 1 Distribution of the sample as a function of age of subjects at the time of cochlear implantation and age group assigned

Group	Age of implantation, y	Patients, No.	Patients per group, No.
I (≤2 years)	1	5	26
	2	21	
II	3	6	6
III	4	6	6
IV (≥4 years)	5	1	19
	6	1	
	7	1	
	8	6	
	9	2	
	10	5	
	11	1	
	12	1	
	13	1	
Total		57	

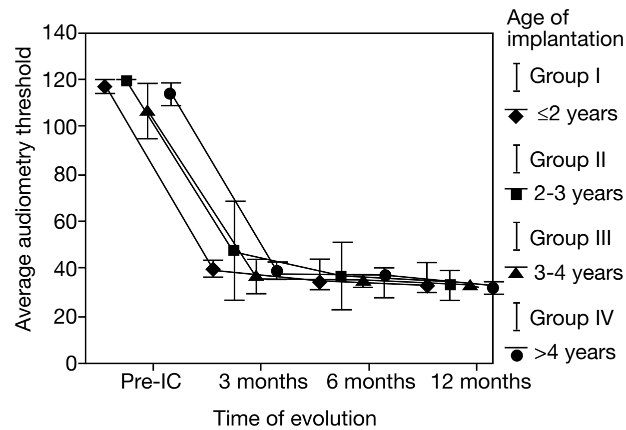

Figure 1 Representation of the average and 2 standard deviations of the average audiometric thresholds (at 250, 500, 1000, 2000, and 4000 Hz) for each of the groups of children according to age of implantation (I: ≤2 years; II: 2-3 years; III: 3-4 years; and IV: ≥4 years). In the absence of response to maximum stimulation provided by the audiometer, a threshold of 120 dB was assigned. There is a similar trend for the different groups in relation to audiometric thresholds, and no statistically significant differences were detected between them.

Table 2 Statistical significance of the comparisons through the Student t tests between the different groups established according to age of implantation

		P value of statistical significance for the comparison between Groups				
		Group I vs. Group II	Group II vs. Group III	Group III vs. Group IV	Group I vs. Group III	Group II vs. Group IV
Audiometry	3 months	.19	.3	.58	.47	.16
	6 months	.5	.77	.56	.88	.92
	12 months	.96	.91	.74	.93	.69
Disyllabic test	1 year	.42	.6	.001[a]	.4	.17
	2 years	.21	.1	.0004[a]	.84	.0017[a]
	3 years	–	–	.002[a]	.44	–
	4 years	–	–	.002[a]	.79	–
	5 years	–	–	.02[a]	.17	–
Phrase test	1 year	.56	.6	.0003[a]	.32	.1
	2 years	.24	.26	.00001[a]	.68	.15
	3 years	.041[a]	.18	.001[a]	.31	.2
	4 years	–	–	.017[a]	.56	–
	5 years	–	–	.65	.56	–
Nottingham scale	1 year	.2	.26	.036[a]	.41	.77
	2 years	.012[a]	.15	.015[a]	.62	.83
	3 years	–	–	.002[a]	.67	–
	4 years	–	–	.003[a]	.98	–
	5 years	–	–	.004[a]	.73	–

–indicates magnitude of the sample not sufficient to carry out the statistical test.
[a]*P* value of statistical significance <.05.

occasional differences between groups I and II in the third year of evolution (Table 2).

As for the study of language using the Nottingham Scale, we once again note that children implanted early (before age 4) develop better skills than those implanted after 4 years of age (Figure 4). We can appreciate that these children reach a roof in their progression at 3-4 years from the onset of stimulation and have a clear difficulty to obtain the highest test scores. We found statistically significant differences between groups III and IV in all assessments

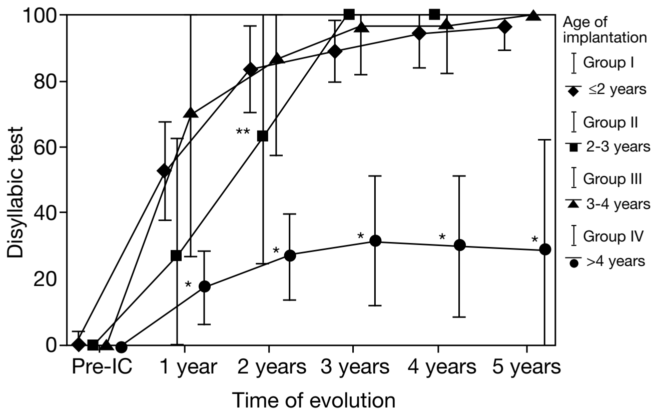

Figure 2 Average (95 %confidence interval) of the disyllabic test applied at different times of the evolution to the 4 groups of children according to age of implantation. The 4 curves show the evolution of each of the 4 groups (I: ≤2 years; II: 2-3 years; III: 3-4 years, and IV: ≥4 years).
[a]$P<.05$ between groups III and IV.
[b]$P<.05$ between groups II and IV.

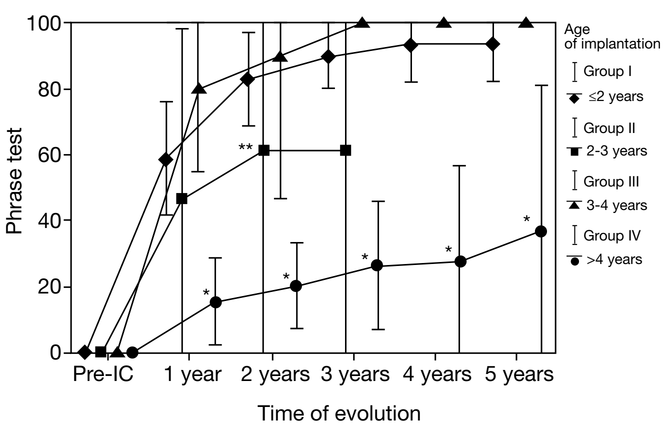

Figure 3 Average (95 %confidence interval) of performance measured by the phrases without lip-reading test. A rapid growth in performance was observed for groups I and III. The performance is shown to be clearly lower in group IV. Group II shows intermediate results, while emphasizing the wide range of its confidence intervals, probably due to the scarcity of the sample in that group (I: ≤2 years; II: 2-3 years; III: 3-4 years; and IV: ≥4 years).
[a]$P<.05$ between groups III and IV.
[b]$P<.05$ between groups II and IV.

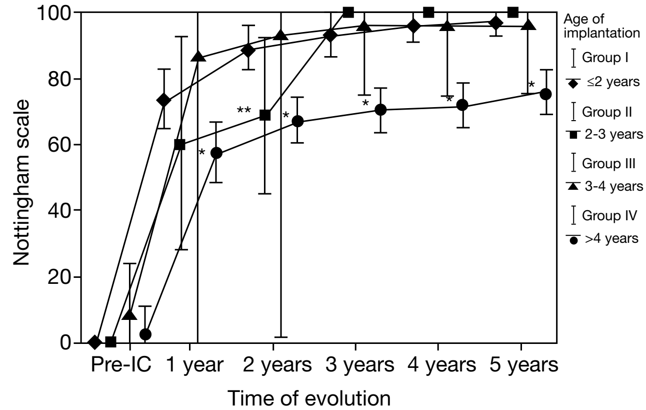

Figure 4 Average (95 % confidence interval) in the Nottingham scale. There is a difference which is statistically significant between groups of children implanted before age 4 and implanted after this age (I: ≤2 years; II: 2-3 years; III: 3-4 years; and IV: ≥4 years).
[a]$P<.05$ between groups III and IV.
[b]$P<.05$ between groups II and IV.

made, and, occasionally, between groups I and II in the evaluation of the second year of follow up (Table 2).

Discussion

The evidence from the present study shows that, judging from the experience at our centre, there is a critical period for cochlear implantation in children with prelingual profound hearing loss. The design of the study has allowed for the exclusion biases that could mask the results, such as including only subjects without morbidities concomitant to hearing loss as well as only prelingual hearing loss. In addition, all children were operated on by the same surgeon and the device programming methodology was the same in all cases. Furthermore, only those children implanted with devices from the same manufacturer were included.

We obtained a relatively high average age of implantation, 4.56 years, which is due to the spread of the data in our sample; nonetheless Table 1 shows that the mode of implementation is around 2 years of age. Indeed, this is the age at which children are typically implanted at our centre; however, some children are operated on at older ages due to unfavourable socio-demographic factors and this increased the average age of implantation.

The data resulting from our analysis shows a clear difference in performance between groups of children implanted before 4 years of age and implanted later, and this difference has been demonstrated with statistically significantly ($P<.05$) in all tests analyzed in nearly all evaluations. The study using the Student *t* test on pairs of groups has also identified possible differences amongst the younger groups of implanted children, although no solid trend has been proven in this direction, only occasional differences. These occasional differences have always referred to the comparisons of group II with others. As discussed previously, this group is represented by only 3 subjects with a follow-up from year 2, and therefore a larger sample would be required to confirm these results.

Our results are consistent with those from previous studies[12] which found, through the electrophysiological analysis of P1 wave latency, used as an index of maturation of the auditory pathway, that there are clear differences in development between children implanted before 42 months of life and those intervened later. Those authors place the limit of the critical period at 3.5 years of age, but suggest that in certain cases it could be extended up to 7 years of age.

Fryauf-Bertschy et al[18] analyzed 34 children with prelingual deafness carrying cochlear implants and state that auditory performance is inversely related to age of implantation. In accordance to this study, they found that children implanted between 2 and 5 years obtained higher scores than those implanted later.

Other works[11,19] have shown that children with hearing loss develop a lapse in language development compared with those with normal hearing, and that once auditory stimulation has been established language begins to develop with near normal growth when this takes place in early stages. We have also noted this fact, since children who have been implanted early on reach the highest scores on the tests taken in the first 2-3 years of use of the cochlear implant. However, this is not detected in those implanted at ages over 4 years, and in fact they show a roof in their development. Therefore, this indicates that children with congenital hearing loss can develop language skills at a rate close to normal as long as the afferences are established early enough in life. Thus, Svirsky et al[11] compared the language skills in children with normal hearing and those suffering prelingual hearing loss who were implanted at 2, 3, and 4 years. This work showed differences in children implanted at the three ages and it also found that children implanted between 12 and 24 months are 1 standard deviation below the average of those with normal hearing; those implanted between 25 and 36 months are within 2 standard deviations and those implanted between 37 and 48 months are below these limits. This publication does find differences between implantation at ages below 4 years and finds the best results when the implantation is performed at an age below 2. We have not detected differences in such young ages, possibly due to the small size of the sample of children in groups II and III, as already discussed.

However, the effect of language performance deterioration with age of implantation which was argued by different authors, and highlighted again by our data, was not observed in the analysis of the average audiometric thresholds. This suggests that although activation of the peripheral auditory pathway can be achieved efficiently at different ages of implantation, the acquisition and development of language achieve their best scores when pathway activation is performed at an early age. This is because language acquisition requires a plastic brain, capable of making new connections and relationships to acquire complex skills such as speech, and not just peripheral afferents.

Apart from these functional data, it is necessary to note that the optimal age must also consider parameters which are external to the patient. In this context we highlight the importance of both the introduction of universal screening for hearing loss in newborns as well as the latest advances in audiological diagnostic techniques, which allow the confirmation of hearing loss in a more reliable and secure manner at early ages. In our team, brainstem auditory potentials in stable state[20] and experience in conducting subjective tests have provided reliable diagnosis at very early ages.

It is also essential, before making any recommendation on the desirability of early cochlear implants, to consider a complete analysis of the risks and benefits. Retrospective studies which analyzed medical records of children implanted at very early ages[21] have found no increased risk during anaesthesia or a more complex surgical procedure. It should be pointed out that elective otologic surgery in children under 1 year can be performed safely in institutions that have continuous experience and available perioperative care units. Close collaboration is required between surgeon and anaesthesiologist in order to ensure the safety of these very young children.

Finally, the critical age to implant should not be considered as an accurate, static or universal time, but as an approximate age, since each individual may present differences in brain evolution. In fact, one aspect which has been previously highlighted[11] is the evidence of a large variability between subjects. Even though different age groups show important differences, each group may contain certain individuals with higher performances than expected. We have also found a high variability in results between the data of children implanted at similar ages for which we could not determine a clear cause. We also noted that, although cochlear implantation at an early age may be the most beneficial, excellent results can also be achieved at older ages. Therefore, the establishment of a critical period should not lead to the exclusion, as candidates for cochlear implant, of children diagnosed later or those forced to later implantation due to additional circumstances. Furthermore, although the performance is lower as the implementation takes place later, all subjects showed improvement over pre-implant condition.

All this suggests that future lines of research in cochlear implant should be directed towards trying to explain the variation in performance found among subjects who seemingly share similar prognostic factors. Perhaps studies on the involvement of higher-level cognitive processes or other unexplored variables may indicate whether there are special procedures that may apply when the alleged critical period of a subject has already been surpassed.

Conclusions

We establish that the optimal age to implant children with profound congenitally deafness is before 4 years of age.

There is no minimum age limit for early implant in children, and the fundamental limitations are the diagnostic confidence and the possibility of providing appropriate perioperative care at such young ages.

Even setting the critical period at a particular age, older children should not be excluded from cochlear implantation since, although it appears that the prognosis is more discreet, they still derive a significant benefit with respect to lack of implant.

The reasons for the variability found in children implanted at similar ages still remains to be clarified.

Conflict of interests

The authors have indicated no conflict of interests.

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