CASE STUDY

Congenital Disorders of Glycosylation: First Deaf Patient Treated With a Cochlear Implant

Trastorno congénito de la glucosilación: experiencia en el primer paciente hipoacúsico tratado con implante coclear

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Received 10 April 2012; accepted 4 September 2012

Clinical Case

We present the case of a 15-year-old girl, the offspring of related parents. At birth, the child presented facial dysmorphism, nystagmus, feeding problems and encephalopathy. Later on, she displayed psychomotor delay, obesity, microcephaly, progressive partial optical atrophy, cerebellar syndrome with truncal ataxia and paroxysmal epileptic attacks. Imaging studies showed a delay in neuronal myelination. ¹

For the syndromic diagnosis, we established the carbohydrate-deficient transferrin (CDT) and its isoforms using immunoturbidimetry, isoelectric focusing (IEF), immunofixation and Coomassie® brilliant blue staining. We also analysed lipid-linked glycosaccharide in fibroblasts and the 9 exons of the dolichol-phosphate-mannose synthase 1 (DPM1) gene using D-HPLC, ² with it being a homozygote for a new mutation in the exon 9 DPM1 gene.

The patient was referred to our unit from the Paediatric Neurology Unit in our hospital, because of suspicion of hearing loss at the age of 11 years.

She presented language acquired as canonical babbling (goong and laaing), as well as echolalic patterns of speech and behaviour. In addition, she presented progressive loss of visual acuity.

For auditory assessment, conditioned audiometry was performed during 3 consecutive days at about 30 min per session, with 2 speech therapists-1 in the booth and another in the pre-booth-and (as motivation) the patient’s mother in the pre-booth as well. The sound was conditioned with warble tones; the reception signal was a slap on the hand of the speech therapist in the booth and positive reinforcement was given as applause, caresses and congratulations. To ensure voice perception and understanding of simple orders, we used the mother placed outside the range of residual vision and/or physical contact with the patient. We used a CD-ROM regulated by audiometer for perception of the children’s song. The patient’s behaviour was observed for the background sounds.

We carried out single and binaural audiometry, the battery of sound instruments, corporal and background sounds and voice threshold. The studies indicated that the auditory threshold was below 75 dB in the frequencies assessed (500, 1000, 2000 and 4000 Hz). It was difficult to establish the existence of a preference for 1 ear over the other, especially because of the patient’s characteristics. She showed a response to voice, but there was no verbal discrimination; the corporal expression of her interlocutors was fundamental for communication.

The study using transient otoacoustic emissions showed a response at 27.45 dB SPL in the left ear and at 24.77 dB SPL in...
the right. The background noise oscillated between 22 and 29 dB SPL, with a mean intensity of stimulation of 84 dB SPL and SNR-10 dB in at least 3 frequencies and always above 3 dB.

Brainstem auditory evoked potential was carried out using a monaural click at intensities from 105 to 60 dB with contralateral masking noise and register in the ear lobe: at supramaximal intensities of 95, 100 and 105 dB, an irregular response was obtained with increased latencies of components, with the results being compatible with a bilateral cochlear hearing loss having a response loss at 95 dB.

An imaging study was performed using CT in which no morphological anomalies were revealed in cochleas, vestibules or semicircular canals. Middle ear cavities were well developed and pneumatized.

The patient was proposed for a Freedom™ type cochlear implant in the right ear in May 2008. The peri- and postoperative evolution was satisfactory. In the following months, the patient initiated intensive speech rehabilitation adapted to her situation.

At present, the patient’s communicative ability is developing in a satisfactory manner, in agreement with her cognitive capabilities: responds to her name, to simple orders given in daily language, distinguishes different voices of people in her family and school environment, and reacts to environmental sound stimuli. She reproduces at speech intensity just by hearing in open context from single syllable to multiple syllable words. Binaural conditioned audiometry shows an auditory threshold of 45 dB. The patient reproduces the linguistic sounds /α/, /æ/ and /e/, but not /i/ or /s/. Her attention deficit makes a complete discrimination test impossible. She detects and sings known songs after hearing them at 45 dB. She asks for the implant every morning, lets someone know when the batteries go dead and gets angry if the implant is taken away from her.

Discussion

Congenital disorders of glycosylation represent a type of innate mistakes of the metabolism of autosomal recessive inheritance. They affect the synthesis of the glycans of glycoproteins. Various types of congenital disorder of glycosylation (CDG) that affect N-glycosylation have been described, based on the location of the deficient enzyme: CDG I, from affection of the synthesis and transfer of a single oligosaccharide to the peptide chain, and CDG II, which corresponds to errors in maturation of the glycan chain. Clinically, they manifest heterogeneously, generally with multi-organ involvement.

The type CDG Ia, the most frequent and best known, includes neurological manifestations with psychomotor delay and culvulsive episodes, skin problems, facial dismorphia facial and digestive, heart and kidney involvement. The second type, CDG Ib, joins severe enterohematological involvement with hyperinsulinemic hypoglycaemias and, at times, thromboembolic events, without any neurological or cutaneous involvement.

The case we present is that of a patient with CDG type i.e. produced by deficit in DPM1, an enzyme related with assembling the glycans in the membrane of the endoplasm reticule. The enzyme DPM1 is composed by 3 subunits. Only mutations in the catalytic subunit have been described, which occurred in 4 patients from 3 families. The clinical features that this deficit produces are: infantile encephalopathy, postnatal microcephaly, hypotonia, dysmorphic fasciae, oligophrenia, optic atrophy and brain dysfunction without cerebral atrophy. Our patient presents a syndrome that is less clinically severe than the cases described previously.

Diagnostic confirmation of these disorders requires elevated diagnostic suspicion, specific analyses and assessment by specialists in genetics and metabolic diseases.

We have not been able to verify the aetiology of our patient’s auditory deficit. The specific association of hearing loss with CDG is not described in the literature. Furthermore, our patient did not present risk factors such as family antecedents, perinatal infections, prematurity, hyperbilirubinemia, exchange transfusion, exposure to ototoxic, meningitis, perinatal hypoxia or need for mechanical ventilation. However, she did show certain language acquired in the form of canonical babbling, whose utterances presented characteristics acquired from perceived speech. This makes us consider acquired hearing loss, from perhaps some 6–9 months of age.

Detecting hearing loss can go unrecognised in the context of these patients’ multiple pathologies. However, early diagnosis and treatment of the hearing loss can mean significant improvement in their adaptation to their surroundings. We attribute delay in patient diagnosis to the lack of an early hearing loss diagnosis programme at the time the patient was born. In addition, it is possible that the diagnostic suspicion and referral to our service was delayed because the patient’s communicative deficit was attributed to her psychomotor delay.

This is the first patient with CDG treated with a cochlear implant. The audiological study of this patient was difficult due to her maturation delay, attention deficit and visual capacity. Various sessions with high levels of motivation were required to stimulate the auditory threshold. The indication of objective studies using otoacoustic emissions and brainstem evoked potentials were essential.

The cochlear implantation in this patient can be considered controversial, given her psychomotor delay and the absence of prior auditory stimulation. In the last several years, the patient has experienced an important worsening of her visual capacity due to progressive optic atrophy, so the cochlear implant could be considered justified to avoid her social isolation.

Placement of the cochlear implant was not made more difficult by any anatomical anomalies and her peri- and postoperative evolution was satisfactory.

The functional auditory result has meant an improvement in the patient’s quality of life: she responds to her name, detects, identifies and discriminates sounds in the environment, and reproduces ordinary words at speech level. It should be supposed that this output has been influenced by the neurological deficit of the patient in her rehabilitation, as well as the delay in treatment of her hearing loss.

It would be recommendable to develop diagnostic techniques adapted for patients with problems of attention and psychomotor development. Early placement of cochlear implants in deaf children with CDG in the future would
provide us with more information about their long-term results.

Conflict of Interests

The authors have no conflicts of interest to declare.

Acknowledgements

We would like to thank Margarita Torres and Isabel Chicharro for their thorough and dedicated audiological assessment and Juan Manuel Galván for his inestimable help in the literature search.

References


