Early Treatment with Growth Hormone (GH) and Rehabilitation Recovers Hearing in a Child with Cerebral Palsy

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Abstract: Neonatal hearing loss is one of the most common anomalies and is frequently associated with delivery problems. The effects of growth hormone (GH) on brain regeneration after an injury are well known. This paper looks at a male child diagnosed with cerebral palsy, psychomotor affection, left spastic hemiparesis, and bilateral sensorineural hearing loss after fetal distress due to ruptured membranes before the delivery of more than 30 hours of evolution and several episodes of severe hypoglycemia. From 3.5 months of age, we treated him with GH (0.04 mg/kg/day), Melatonin (5 mg/day and 6 months later 10 mg/day) and rehabilitation, for a period of 14 months; at discharge, the child fully recovered all the disabilities produced by his cerebral palsy, including normal hearing; GMFM-88 increased from 7.84% to 48.23%; Battelle scores increased from 2 to 9 after 7 months of treatment, and to 30, 1 year after discharge. Most likely hearing loss was recovered due to the effect of GH on the production of hair cells from stem cells (only present in very young children) in the cochlear sensory epithelium. This is the first case of recovery of hearing loss in humans after GH administration. Moreover, GH administration is useful and safe for early treatment of cerebral palsy.

Keywords: hearing loss; cerebral palsy; growth hormone; auditory stimulation; physiotherapy

1. Introduction

For years, we have known that a significant bilateral hearing loss is present in approximately 1 to 3 per 1000 newborns in the population of children born normal, and in approximately 2 to 4 per 100 babies that after delivery have to receive intensive care [1]. The standardization of the early detection programs, fundamentally with the auditory brainstem response potentials (ABR), has allowed for adequate detection and treatment in a critical period in the psychomotor development of the baby [2]. Although in most cases the etiology is unknown, several risk factors have been identified that favor the development of newborn hearing loss [3]. For example, auditory function in newborns admitted to neonatal intensive care units (NICU), especially those treated with oxygen or antibiotics, should be evaluated early to detect the possibility of hearing impairment, as they are at much higher risk of suffering it; therefore, any unnecessary oxygen therapy or antibiotics administration should be avoided in these children [4].
Fetal distress leading to hypoglycemia is an important prognostic factor for developing hearing loss. The outcome depends on various factors such as the duration, severity, utilization rate of cerebral glucose, and cerebral blood flow velocity. Apart from hearing loss, fetal or neonatal hypoglycemia can produce visual disturbances, cognitive deficits, and even epilepsy [5]. In fact, neonatal hypoglycemia is a cause of multiple neurological disorders [6,7] and a risk factor for damage to the inner ear in newborns through various metabolic mechanisms, especially if it is maintained over time [8,9]. Therefore, children born to diabetic mothers, which can produce neonatal hypoglycemia, have a greater risk of developing hearing loss [10]. In addition, in a significant percentage of cases (around 20%), babies with hearing impairment manifest one or more associated comorbid conditions; this is the case of children with cerebral palsy (CP). In these CP children, bilateral sensorineural hearing loss is also common [11]. Hence, to improve prognosis, early detection and early treatment are essential in these cases.

Interestingly, alterations in growth hormone (GH) secretion or its signaling pathways may also affect the hearing function [12-14]. Children with GH deficiency frequently exhibit hearing loss. In this situation, the impairments are commonly bilateral; mixed or sensorineural hearing loss are the most frequent types. Patients experience more chronic otitis media and episodes of Eustachian tube dysfunction compared to the general population [12]. Adults with an isolated deficit of GH may have selective sensitivity to some common sounds (misophonia) and hearing loss. The auditory disability is mainly sensorineural and affects middle and high frequencies. Other audiological findings in this group of patients show the absence of stapedial reflex and transient evoked otoacoustic emissions [13]. In addition, individuals affected with Laron syndrome have mild hearing loss, absence of acoustic reflexes, and hyperacusis [14,15].

GH has been shown to play a key role in the regeneration of different parts of the body [16]. GH promotes the recovery of multiple musculoskeletal and splanchnic structures, and several studies have shown promising results in angiogenesis and neurogenesis, activating or repairing the brain and spinal cord after an injury [16-20]. In previous studies, our group demonstrated that GH treatment and rehabilitation were effective in the recovery of children with cerebral palsy [21,22], probably through the induction of neurogenesis by GH [23]; therefore, in this study we analyzed the effect of early treatment with GH and rehabilitation in a child 3.5 months old with CP and marked hearing loss, attempting to recover the auditory loss and other existing motor and cognitive deficits.

The results obtained indicate that this early treatment completely recovered the cognitive, motor and hearing deficiencies initially observed without the administration of GH producing any adverse effect.

2. Case Presentation Section

2.1. Medical History

The patient was a male 3.5 months old, with CP, who came to the Foltra Medical Center for medical treatment and rehabilitation. Pregnancy occurred due to in vitro fertilization with loss of his twin at week 11 of gestation. The glucose tolerance tests of the mother were normal, as were the ultrasound follow-ups. At week 30 of gestation, the mother suffered preeclampsia, so the lung maturation of the baby was induced. The child was born at 36 + 4 weeks of gestation after an urgent cesarean section due to fetal distress produced by the rupture of membranes over 30 h of evolution, with a high infectious risk. At birth, the Apgar score was 9/10, weight 3.240 kg, size 40 cm, and cranial perimeter 34 cm, within the limits of normality. Immediately after birth, he presented untreated transient hyperbilirubinemia, without jaundice, and several episodes of hypoglycemia lasting more than 5 h that required admission to the neonatal intensive care unit (NICU) for 6 days. During his stay in the NICU, neuro-ultrasound and electroencephalography (EEG) were performed, which were normal, and metabolic tests and hearing tests with otoacoustic emissions were passed. At the time of discharge from hospital (15 days), the baby was diagnosed with infantile cerebral palsy with psychomotor retardation (left spastic hemiparesis, predominantly crural, and facial hypotonia). There was no data in the clinical history of infection or ototoxic antibiotic treatment
and/or any other subsequent complication. During the pediatric check-up, a marked absence of visual fixation was observed. After 2 months, an evaluation of the auditory response of the brainstem (ABR) was made by means of a monaural click with a contralateral mask of +30 dB; 1kHz tympanometry was normal in both ears. Therefore, the diagnosis was neurosensory hearing loss with bilateral thresholds at 50 dB (Figure 1).

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<td>ms</td>
<td>ms</td>
<td>ms</td>
<td>ms</td>
<td>pps</td>
</tr>
<tr>
<td>Left Ear - Audiometry</td>
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<td></td>
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<td></td>
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<tr>
<td>1 A1 - Cz</td>
<td>90nHL</td>
<td>2.77</td>
<td>5.15</td>
<td>7.06</td>
<td>2.38</td>
<td>1.92</td>
<td>4.29</td>
<td>11</td>
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</tr>
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<td>60nHL</td>
<td>8.15</td>
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<td></td>
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<td>50nHL</td>
<td>8.58</td>
<td></td>
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<td></td>
<td></td>
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<tr>
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<td>No response</td>
<td></td>
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<td></td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>1 A2 - Cz</td>
<td>90nHL</td>
<td>2.96</td>
<td>5.15</td>
<td>6.77</td>
<td>2.19</td>
<td>1.62</td>
<td>3.81</td>
<td>11</td>
</tr>
<tr>
<td>2 A2 - Cz</td>
<td>60nHL</td>
<td>7.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 A2 - Cz</td>
<td>50nHL</td>
<td>4.13</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5 A2 - Cz</td>
<td>40nHL</td>
<td>No response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Auditory brainstem responses at 2 months of age, per monaural click with contralateral masking of +30 dB. Note that wave I falls outside the normal latency levels, but there is a normal wave V latency at higher intensities. Auditory thresholds at 50 dB, with no response to lower values. Intervals within normality, without retrocochlear signs. Stim.: Stimulation; Rep. Rate: repetition rate; ms: milliseconds; Cz: reference electrode in the vertex; A1: registration electrode; A2: the registration electrode in the right ear; HL: normalized hearing level; ABR: Auditory brainstem responses.

At 3 months of age, an EEG video showed no electroencephalographic abnormalities, while a magnetic resonance imaging (MRI) reported slight cortical retraction with increased subarachnoid space and mild ventricular dilation (data not shown). At admission in our Center (three and a half months), the initial motor exploration showed increased stretch reflexes, the persistence of primitive reflexes (particularly the Moro reflex), and facial hypotonia. There was left spastic hemiparesis, predominantly crural. The patient showed a delay in expressive language (little babbling and poor communicative intention) and very poor tracking of auditory and visual stimuli.
2.2. Blood Analysis

Before beginning GH treatment, a blood test was performed. This blood test was repeated every 3 months until discharge, 14 months after admission, and again when the child came for a revision 14 months after discharge and at 5 years of age. Results from these blood analysis are shown in Table 1.

Table 1. Main plasma values (hematology, biochemistry, hormones) at admission (Adm.) and at 3-month intervals after beginning the treatments and at discharge (Dis.), and normal values for the age of the patient. Note that at admission, total cholesterol, triglycerides, creatinine, GOT (aspartate aminotransferase) and CPK (creatine phosphokinase) were at values over the upper limit of normality. Plasma cholesterol and creatinine already had normal values after the first 3 months of treatment, while GOT after decreasing after 3 months of treatment, again increased 3 months later and remained slightly elevated until discharge. This was most likely due to levels of triglycerides in plasma which were always higher than normal values due to high caloric intake at the expense of fatty foods with which his mother fed him. At admission, the plasma CPK had high values, probably due to the existing spasticity, but 9 months after starting the treatment it was already at normal values. Thyroid hormones and cortisol were always at normal values (data not shown). IGF-I: Insulin-like growth factor I. IGFBP3: Insulin-like growth factor binding protein 3. M: months.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adm.</th>
<th>3 Months</th>
<th>6 Months</th>
<th>9 Months</th>
<th>12 Months</th>
<th>Dis.</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>4.62 × 10¹</td>
<td>4.75 × 10¹</td>
<td>4.97 × 10¹</td>
<td>4.48 × 10¹</td>
<td>5.15 × 10¹</td>
<td>4.96 × 10¹</td>
<td>4.20–5.85/µL (10¹)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>34.70</td>
<td>36.60</td>
<td>38.20</td>
<td>33.80</td>
<td>38.80</td>
<td>37.20</td>
<td>30–42%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.50</td>
<td>12.10</td>
<td>12.50</td>
<td>11.30</td>
<td>12.90</td>
<td>12.60</td>
<td>10.00–13.80 g/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>90.6</td>
<td>93</td>
<td>104</td>
<td>78</td>
<td>73</td>
<td>85</td>
<td>60–110 mg/dL</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>224.5</td>
<td>172</td>
<td>185</td>
<td>173</td>
<td>152</td>
<td>169</td>
<td>50–175 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>330.6</td>
<td>189</td>
<td>148</td>
<td>102</td>
<td>112</td>
<td>105</td>
<td>31–90 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.73</td>
<td>0.5</td>
<td>0.3</td>
<td>0.45</td>
<td>0.33</td>
<td>0.39</td>
<td>0.20–0.45 mg/dL</td>
</tr>
<tr>
<td>GOT</td>
<td>42.4</td>
<td>35.2</td>
<td>65</td>
<td>41.1</td>
<td>43.5</td>
<td>40.8</td>
<td>0.50–40 U/L</td>
</tr>
<tr>
<td>CPK</td>
<td>325</td>
<td>352</td>
<td>338</td>
<td>158</td>
<td>195</td>
<td>186</td>
<td>195 U/L</td>
</tr>
<tr>
<td>IGF-I</td>
<td>57</td>
<td>94.3</td>
<td>144</td>
<td>163</td>
<td>147</td>
<td>152</td>
<td>27–172 ng/mL</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>3.8</td>
<td>4.1</td>
<td>4.2</td>
<td>4.8</td>
<td>3.9</td>
<td>3.6</td>
<td>2.6–5.8 ng/mL</td>
</tr>
</tbody>
</table>

In the revisions carried out 14 months after discharge and at 5 years of age, all values were normal.

2.3. Medical Treatments

GH (Nutropin, Ipsen Pharma, Barcelona, Spain) was given at a standard dose of 0.04 mg/kg/day, 5 days/week, sc, at 9.00 am, for 3 months. After 1 month resting, the same GH treatment, adjusted to the weight of the patient, was resumed for another 3 months. This pattern was repeated until discharge. In addition, melatonin (MT) (5 mg/day for 6 months and then 10 mg/day until discharge), prepared by master formula and administered orally, was given without interruption before going to bed at night.

This medical treatment was carried out in accordance with the protocols followed in our Medical Center and in compliance with Spanish legislation for the use of GH and MT “off label” (Spanish legislation: Royal Decree 1015/June 2009; Declaration of Helsinki: June 1964, lastly amended in October 2013; Ethic Code of Foltra: 2012-x-08) and the Code of Ethics of the World Medical Association (Declaration of Helsinki). Signed informed consent to use GH and MT was obtained from the patient’s mother (her legal representative).

No secondary side effects were observed due to GH or MT, neither at discharge nor in the following revisions.

2.4. Rehabilitation and Results
Rehabilitation consisted of daily sessions (5 days/week, 45 min each) of Physiotherapy, Neurostimulation, Integrative and Neurosensorial stimulation (EINA), and Speech Therapy.

2.4.1. Physiotherapy

At admission, the patient presented moderate spasticity (score 1–2 in the modified scale of Ashworth) in some muscles of the left hemibody, such as shoulder abductors, wrist and finger extensors, supinator of forearm, hip adductors, and ankle and finger extenders. Spasticity was more marked (2) in the lower limb. There was neither the facial optical reflex nor the facial acoustic reflex. The Gross Motor Function Measure (GMFM-88) (the instrument most commonly used to measure change in gross motor function over time in children with cerebral palsy) score was 7.84%. Therefore, the initial objectives were: to achieve the acquisition of a stable prone position, reach the midline and exceed it, and improve trunk control. Moreover, in the lower limb, there was only movement in the right leg, and it was a movement directed more towards abduction than towards extension.

The spasticity soon disappeared, so that after 6 months of treatment the value on the Ashworth scale was 0 in all muscle groups. Progressively, the patient was gaining functionality on the affected side and integrating this in his body; thus, at the time of discharge, the GMFM-88 score had increased to 48.23%, a value normal for his age. These motor changes are shown in Figure 2.

![Figure 2](image_url)

**Figure 2.** Motor evolution of the patient as indicated by the scores (%) reached in the Gross Motor Function Measure (GMFM-88) scale. Note that the value achieved at discharge (14 months) corresponds to the mean of normality (50.26 ± 4.36, mean ± SD) in children of similar age to that of the patient. In the revisions carried out 14 months and 5 years after discharge, no motor abnormalities existed.

2.4.2. Neurostimulation

The evolution in this area was very good. The child began to carry out a greater visual follow-up, as he improved in gross and fine motor skills, beginning to use both hands in performing a task. In addition, he improved cognitively and acquired the ability to perform simple social games. Therefore, at discharge, his level of development was already very close to that corresponding to his chronological age, even surpassing it in some areas, as the Battelle scores indicate. These results are shown in Table 2.
Table 2. Scores achieved in the Battelle Developmental Inventory Screening Test (BDIST) at admission (3 months and 15 days), after 7 months of treatment (10 months and 19 days) and 14 months (28M15d) after Discharge. Note the improvements in practically all areas of the test during the treatment, but also the marked increase in these scores observed when the patient came for a revision 14 months after discharge, so that despite the fact that the patient was 28 months and 15 days old, his age of development corresponded to 30 months.

<table>
<thead>
<tr>
<th>Area</th>
<th>3 Months and 15 Days</th>
<th>10 Months and 19 Days</th>
<th>28 Months and 15 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social/Personal</td>
<td>2</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td>Adaptive</td>
<td>2</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Gross motor</td>
<td>3</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>Fine motor</td>
<td>3</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Total Motor</td>
<td>3</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Receptive communication</td>
<td>1</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Expressive communication</td>
<td>1</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>Total Communication</td>
<td>1</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Cognition</td>
<td>3</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>9</td>
<td>30</td>
</tr>
</tbody>
</table>

2.4.3. Integrative and Neurosensorial Stimulation (EINA)

Initially, and given the age of the patient and his moderate hearing loss, this therapy was focused to specifically work on musical sonic return and sonic birth (using the voice of his mother, previously recorded on a CD). This type of stimulation, specifically useful for very young patients, was carried out in two blocks, with a week of separation between them. Then, a third block of auditory stimulation was performed, using only filtered Mozart music and Gregorian chants. The objective of this third block was to integrate what was worked on in the previous blocks and to enhance the interhemispheric relationship [24]. At the end of this block, an audiometry was performed, which resulted in a 100% recovery of hearing loss in both ears, as Figure 3 shows.
ms: milliseconds; Cz: reference electrode in the vertex; A1: registration electrode; HL: normalized hearing level; ABR: Auditory brainstem responses.

The exam, carried out by the Otolaryngologist who explored the child when he was 2 months old, indicated that (as it had been seen previously) 1kHz tympanometry was normal in both ears. The new exam indicated that auditory thresholds were now within the normal range and no retrocochlear pathology signs existed. In the following years, new audiometry tests (0.5–4kHz) were again within the normal range (pure tone average: 20 db right ear/23 db left ear at 4 years old and 15 dB right ear/13 dB left ear at 5 years old).

In addition, at this time, visual evoked potentials were performed showing normal conduction from the retina to the visual cortex.

2.4.4. Speech Therapy

As indicated, at admission, the patient had moderate bilateral hearing loss; perhaps because of this his babbling was scarce and not audible, and he had very little communicative intention. He did not imitate. He also presented dysphagia for semisolids and only sucked. There was facial hypotonia and lip asymmetry. Progressively, the situation was changing. The facial hypotonia was disappearing, symmetry appeared in the smile; the patient evolved from a stage characterized by guttural sounds to a stage of non-reduplicated babbling, trying to imitate sounds that were provided during the sessions. Finally, the patient initiated the emission of syllabic strings and began to pronounce the first functional words (mom, aunt, grandmother, dad (in Spanish)). The facial hypotonia disappeared, as well as lip asymmetry. The chewing and swallowing were correct. Therefore, at discharge, in this area the patient reached total normality.

2.4.5. Magnetic Resonance Imaging

At 2 years of age, a new MRI was made; it showed that everything was now normal.

3. Discussion

We first demonstrated that the administration of GH combined with rehabilitation is useful in the recovery of motor and cognitive functions in children with CP [21,22], most likely because the hormone, together with IGF-I, plays a key role in the development of the brain [15,16], even after an injury, facilitating the effects of rehabilitation. Here we describe the positive effects of this treatment performed in a very unusual case of CP, after starting treatment very early after birth.

The patient had very high chances of suffering from an important cerebral affection, since, as described in the Introduction: 1) he was born premature after an urgent cesarean section due to loss of fetal well-being caused by the rupture of the membranes after 30 h of evolution; 2) immediately after birth he suffered several episodes of hypoglycemia for more than 5 hours that led him to stay in the neonatal intensive care unit for 6 days. Moreover, after birth, he had presented transient hyperbilirubinemia. However, the brain ultrasound and EEG were reported as normal, as were metabolic and otoacoustic emission tests. Nevertheless, upon discharge from the Hospital where the child was born, he was diagnosed with cerebral palsy, with psychomotor retardation, left hemiparesis, facial hypotonia, and absence of visual fixation. We do not know the reasons for these apparent inconsistencies (nor do we understand the report of an Apgar 9/10 at birth when there was fetal distress and the delivery was so complex), unless it was suspected that the episodes of hypoglycemia could cause brain damage in the short term. In fact, 2 months later, the auditory response of the brainstem showed a neurosensory hearing loss, and 1 month later an MRI indicated slight cortical retraction with increased subarachnoid space and mild ventricular dilation. Therefore, since apparently there was no hypoxia/ischemia at birth, or Periventricular Leukomalacia due to prematurity, it is likely that neonatal hypoglycemia was the main factor responsible for the development of this CP.
Neonatal hypoglycemia is usually a marker of GH-deficiency, but the child was not GH deficient. We did not analyze it, because provocative tests for studying GH secretion are dangerous in young children, mainly if they suffer from brain damage. In fact, after discharge from our Center he grew normally, and at the age of six, his height was in p70. Therefore, no GH deficiency seems to exist.

Although it is not the objective of this work, it is difficult to explain the occurrence of episodes of hypoglycemia of such a long duration. As mentioned previously, a deficit of GH secretion, perhaps caused by a hypothalamic alteration of the regulatory pathways of this hormone, or their delivery to the somatotrophs, produced by the complicated birth and/or the fetal distress, could justify the hypoglycemia suffered, but as indicated by the subsequent clinical evolution, the patient was not GH deficient. However, hypoglycemia is more likely to have occurred due to the presence of one or more risk factors, such as: prematurity or the fact that the mother had to be treated with β-blockers because of her preeclampsia [5]. In any case, the hypoglycemia suffered may have been the main cause of the hearing loss that the patient presented [5], although we cannot rule out that the development of CP in this child may have occurred as a result of the combination of several factors (fetal distress, complicated delivery) in addition to hypoglycemia.

Since all the typical affectations of the CP were corrected with the treatment carried out, in this discussion, we will focus on the recovery of hearing loss that the patient suffered.

To our knowledge, this is the first case in which GH induced a recovery of sensorineural hearing impairment in a very young child who suffered from hearing loss.

The detection of hearing loss after a normal routine initial hearing evaluation can be explained by 1) a late onset of hearing loss, as consequence of an episode of fetal distress, hypoglycemia included [5,8]; or 2) may be due to a false negative in the first test performed.

Otoacoustic emissions are less sensitive than auditory brainstem response screening [25,26], especially because these tests obviate retrocochlear pathology and auditory neuropathy. However, our patient never showed clinical signs of this type, such as specific prolonged intervals or a very altered/absent registry [25,26]. In a variable, but relatively low percentage of cases (15–30% of positives on initial screening), patients may experience a hearing improvement without treatment [27,28]. Our patient, however, underwent a normal screening test, although he had persistent hearing loss after birth that was objectified by a later ABR at 2 months of age. Moreover, despite his prematurity, the weight, height and cranial perimeter were within the normal percentiles ruling out the existence of a delay in maturation [29–31]. In addition, hearing loss was associated in this case with a psychomotor deficit that improved with the treatments performed. Therefore, a spontaneous recovery does not seem to be the explanation of the results obtained here.

Several studies show the role played by GH in the development of the inner ear, which a priori would support the use of this hormone for auditory recovery. GH receptors are expressed in the inner ear; there is high immunoreactivity for GH and its receptor (GHR) in the otic vesicle of neural chicken cultures on the third embryonic day [32].

In mammals, GH is a canonical hormone that, among many other actions, is involved in the development of different structures of the inner ear, such as utricles, most likely acting via its mediator IGF-I [33]. The cochlear sensory epithelium (CSE) hosts sensory hair cells that act as auditory receptors that transduce sound waves into electrical nerve signals and transmit them to the brain stem and auditory cortex [34]; therefore, they are key to hearing. The loss of these hair cells leads to deafness.

However, in the early stages of postnatal human development, the CSE contains stem cells that show a small regenerative capacity that can give rise to sensory hair cells, a capacity that, physiologically, is being lost as the postnatal development progresses, most likely because of the decrease of production of those stem cells [35]. Interestingly, it has been reported that in adult mice, GH was highly up-regulated in CSE [36], perhaps for attempting the recovery of hair cells. In other species, such as zebrafish, it has been shown that for regeneration of the inner ear, GH increases its expression after stimuli that lead to hearing loss, and that exogenous GH administration induces
hair cells regeneration by stimulating cell proliferation [37,38]. In contrast, when GH antagonists are used, there is a significant decrease in cell proliferation in the inner ear of the zebrafish [38].

The effects of GH on hearing seem to be clear, at least in animal models. In the spiral ganglion of the rat, the nervous structure from which the auditory nerve originates, different concentrations of GH stimulate the growth of neurites and their ramifications, without any alterations in cell morphology [39]. This led the authors to propose that GH may be useful in the treatment of neurodegeneration in the hearing-impaired inner ear.

Although most studies about the effects of GH on the ear have been performed in zebrafish and mice, it seems to be clear that GH expression appears to be localized perinuclearly around erythrocytes in the blood vessels of the inner ear epithelia following trauma. Besides, major histocompatibility complex (MHC) class I and II genes and heavy-chain and light-chain myosins are down-regulated and GH up-regulated in zebrafish’s inner ear. MHC class II molecules are observed in the cochlear cells of adult mice following a damaging event and may promote cell proliferation in the inner ear when there is proliferative capability [37].

It is difficult to extrapolate these results obtained in species lower than what can occur in man. Studies in human adults with hearing loss, treated with GH, would be necessary, but until now there are none, except for a study in girls with Turner syndrome, which is associated with auditory alterations, who received the hormone and androgens and it improved the quality of their speech [40].

However, the effects of GH on many different and very specific neural structures have been widely described (see References [15,16] for review). Some of these effects are directly produced by the hormone, while others may occur by activating other neurotrophic factors. For instance, in chickens, GH, locally produced or exogenously administered, shows neuroprotective actions in neuroretinal cells of chicken embryos by inducing the expression of brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT3) [41,42].

During neuronal development of the inner ear, several neurotrophic factors play significant roles. Among them are IGF-I, BDNF, NT-3 and fibroblast growth factor (FGF); these and many other neurotrophic factors are induced by GH (see [15], for review). These factors not only participate in the neuronal development of the inner ear, but also promote neurite regeneration [38]. For instance, IGF-I acts on supporting cells, activating their proliferation and inhibiting apoptosis [42]. Moreover, IGF-I stimulates other factors that enhance the cochlear repair, such as Netrin 1 (NT-1) [37]. Exogenous IGF-I treatment seems to be a safe and effective therapy with minor side effects for those patients in which the initial treatment with systemic corticosteroids failed in sudden hearing loss [43]. In turn, BDNF is released after hearing damage induced by noise and the activation of its receptor protects the cochlea from this damage [44], but also its exogenous administration protects and recovers the hair cells [45]. NT-3 has demonstrated a regenerative effect on cochlear synapses in several studies following acoustic trauma [46,47].

Apart from GH, the patient was treated with Melatonin to attenuate the inflamed microglia, a typical finding in brain injuries; but MT also has a role in the development of hearing.

Preliminary reports showed that melatonin-forming enzymes, N-acetyltransferase and hydroxy-indole-O-methyltransferase, are synthesized in guinea pigs’ cochlea and are detected in the organ of Corti and the basilar membrane, and also, although to a lesser extent, in the cochlear nerve and vascular stria, including the spiral ligament [48]. Moreover, it has been identified that MT was specifically linked to the cochlear epithelium and the vestibulocochlear nerve in fetal sheep at day 40 of gestation [49]. It has been found that in rats subjected to ischemia, prolongation of the postmortem activity of external hair cells increases after treatment with MT, objectified through distortion product otoacoustic emissions testing (DPOAE), which allows the audiologist to understand how the outer hair cells of the inner ear work. The effect is approximately 350 times more effective than a mixture of antioxidants in terms of their ability to reduce the formation of free radicals [50]. Moreover, a significant difference was found in the malondialdehyde and erythrocyte glutathione peroxidase activity levels between a group treated with melatonin as compared to one that was not treated, and the hearing thresholds exhibited a parallel trend in guinea pigs exposed to noise [51].
In summary, it is likely that the recovery of hearing loss suffered by our patient is due to the treatment followed by GH, either acting directly in the production of CSE hair cells, or in conjunction with the various neurotrophic factors induced by the hormone. In addition, MT may also have played a role in the positive results obtained.

Most likely the early beginning of the treatment was a key factor in the recovery of the patient, not only in the case of his hypoacusia but also in the sequelae of his CP, although in this case, the rehabilitation performed in all the areas affected also contributed significantly to the improvements achieved. Currently, the patient is a fully normal 6 years old boy.

The data from this study support our hypothesis that the earlier a treatment with GH, MT and rehabilitation begins, the more feasible it will be to achieve significant improvements in children with CP [52].

To conclude, this is the first time that hearing loss is recovered with the administration of GH in humans, although it is likely that the age at which treatment begins is a conditioning factor, due to the progressive loss of CSE stem cells with maturation.

4. Conclusions

For the first time, in humans we demonstrated that GH administration is able to recover hearing loss in a young patient with CP. This effect is most likely produced by GH-induced proliferation of CSE hair cells. We propose that an early treatment with this hormone is useful for improving the disabilities found in children with CP, including hearing loss. However, further studies in a larger group of patients are necessary to confirm the results of this case report.


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References

37. Schuck, J.B.; Sun, H.; Penberthy, W.T.; Cooper, N.G.; Li, X.; Smith, M.E. Transcriptomic analysis of the zebrafish inner ear points to growth hormone mediated regeneration following acoustic trauma. BMC Neurosci. 2011, 12, 88.
38. Sun, H.; Lin, C-H.; Smith, M.E. Growth hormone promotes hair cell regeneration in the zebrafish (Danio rerio) inner ear following acoustic trauma. PLoS ONE 2011, 6, e28372.