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Case Report

Cognitive Evolution of a Patient Who Suffered a Subarachnoid Haemorrhage Eight Years Ago, after Being Treated with Growth Hormone, Melatonin and Neurorehabilitation

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Abstract: To describe the cognitive evolution of a patient who suffered a subarachnoid haemorrhage resulting in a total loss of his cognitive functions. The patient was initially treated with GH (0.8 mg/day), melatonin (50 mg/day) and neurorehabilitation 1 year after his brain damage, during 3 months. Then continued with GH (0.5 mg/day, 6 months/year, during 2 years) and melatonin treatments and neurorehabilitation (3 days/week). 5 years later the patient came back to our Centre due to the absence of recent memory and personal and spatio-temporal orientation and he received an intensive specific neurorehabilitation, including EINA (Auditory Stimulation and Neurosensory Integration), together with GH (0.8 mg/day) and melatonin, for 6 months. At discharge of his first treatment period cognitive functions showed very poor changes but these had been improved when he came back 5 years later. A review carried out 8 years after SHA demonstrated that the patient significantly recovered in all the cognitive functions and he was able to live an independent life. GH plays a key role on cognition, including its actions on recent memory. Melatonin, in turn, helps as a neuroprotective agent. A specific neurostimulation must be performed so that the effects of GH can be expressed. Within neurostimulation, EINA seems to play a very important role for enhancing the effects of medical and rehabilitative treatments on brain plasticity.

Keywords: subarachnoid haemorrhage; anterior communicating artery aneurysm; cognitive functions; growth hormone; melatonin; neurorehabilitation; auditory stimulation and neurosensory integration; occupational therapy

1. Introduction

Subarachnoid haemorrhage (SAH) is a devastating situation which puts in a severe risk the life of the patient, because it is a neurological emergence characterized by the extravasation of blood within the central nervous system spaces normally occupied by the cerebrospinal fluid [1]. About 80–85% of SAH, not produced by a traumatic brain injury, occur because the breakage of a cerebral aneurysm [2,3]. In Spain, its incidence (9/100.000 inhabitants/year) is similar to that of many of the first world countries [4]. Since most brain aneurysms develop throughout adult life [5], it is likely that they are a consequence of arterial affectations produced by the current habits of life (nutrition, smoking, alcohol intake, etc.) [6], factors that also imply a risk for the rupture of an existing aneurysm [1].

This concept is supported by the fact that the plasma concentrations of the anti-inflammatory n-3 long chain polyunsaturated fatty acids (Omega-3) are inversely associated to the risk of suffering a stroke [7]; most likely this is due to the beneficious beneficial role that they play on the arterial walls (mainly EPA and DHA), acting on the inflammation and improving endothelial dysfunction [8].

Although approximately only 5% of strokes are produced by SAH, this event implies a high morbidity and mortality. Moreover, it affects people in the middle of his life; in fact, although the incidence increases with age, half of the patients are under 55 years of age when SAH occurs [3,9]; therefore, it usually leads to a long-term dependent daily life, if they survive the initial accident and other strokes do not appear because of delayed cerebral ischemia. All this because apart from the initial brain damage secondary complications exist. Among them vasospasm, rebleeding, hydrocephalus, cerebral oedema, immediate and delayed cerebral ischemia, seizures, cardiopulmonary dysfunction and hyponatremia produced by salt wasting [2,3,10,11]. Therefore, although this is not the main objective of this study, it is necessary to develop effective strategies that prevent the cascade of secondary damage that occurs after a SAH, largely responsible for the disabilities that appear after it, if the patient does not die after that type of bleeding.

In the case of patients with SAH produced by non-traumatic breakage of an aneurysm located at the anterior communicating artery it has been shown that they usually evolve with cognitive impairments [12], as it happened with the patient whose evolution we will describe in this study.

The effects of growth hormone (GH) at the cognitive level are well known since many years ago, although these pioneering studies had been carried out in adult GH-deficient patients [13–19], before and during or after GH-replacement therapy. More recent studies show similar effects of GH on cognitive functions, both in GH-deficient patients [20–22] and in patients with a normal GH secretion [23–27]. Therefore, as in many other cases, in addition to intense neurorehabilitation, we decided to treat a patient who had suffered significant HSA after the rupture of an aneurysm of the anterior communicating artery, with GH and melatonin. In the case of melatonin, we use it because of its known neuroprotective effects as scavenger of many organic radicals and reactive nitrogen species, its protective mitochondrial effects and its effectiveness in the prevention of oxidative damage [28].

We begin to treat the patient one year after having suffered HSA. He was treated intermittently due to family problems at work. In spite of this and despite the serious cognitive problems that presented at admission, eight years after the stroke he recovered practically all his lost cognitive functions and now leads a practically normal life.

2. Case Presentation Section

2.1. Medical History

The patient was a 49-year-old, male, engineer, without any significant medical problems, except hypercholesterolemia, that a year earlier he suddenly experienced a clinical picture of hours of evolution, consisting of severe headaches, vomiting and progressive reduction of consciousness. Upon admission to his referral hospital, he suffered a severe headache, drowsiness and right hemiparesis. Glasgow Coma Scale was 13. An emergency CT-SCAN (CT) identified an intraparenchymal hematoma in the midline of the subfrontal region with subarachnoid and subdural extension in the cerebral sickle and grooves of the convexity bilateral paramedian, ventricular system (lateral ventricles, third and fourth ventricles) and basal cisterns. There was also a right fronto-temporal subdural component. The hematoma produced a mass effect on the ventricular system and a deviation of the midline to the left (Figure 1).

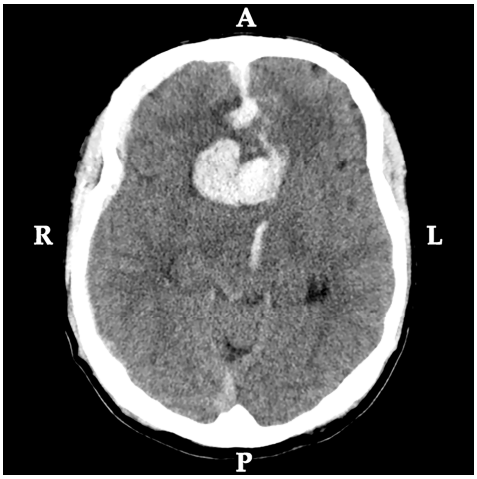

Figure 1. First CT performed shortly after admission. Note the intraparenchymal hematoma in the midline of the subfrontal region with subarachnoid and subdural extension in the cerebral sickle and the grooves of the bilateral paramedian convexity and the mass effect on the ventricular system and the basal cisterns. As a result of the hematoma, the middle line is deviated to the left. A: Anterior; P: Posterior; R: Right side; L: Left side.

An angio-CT identified an aneurysm dependent on the anterior communicating artery (10 mm of maximum anterior-posterior axis, data not shown), whose breakage was responsible for the clinical picture of the patient.

24 h later, urgently, two ventricular frontal drainages were implanted for cerebrospinal fluid release, because a new CT revealed greater amount of intraventricular blood (frontal horns, third ventricle, ventricular bodies and atria, occipital horns and fourth ventricle) as well as a further increase in the size of the ventricular system. In addition, there was a slight increase in intraparenchymal paramedian right hematoma with greater vasogenic oedema adjacent, as well as decrease in the grooves of the bilateral frontoparietal convexity, especially in the more cranial sections in relation to the increase in the mass effect. Small air bubble in the right front horn. However, the deviation from the midline was now smaller than in the previous CT. These findings are shown in Figure 2.

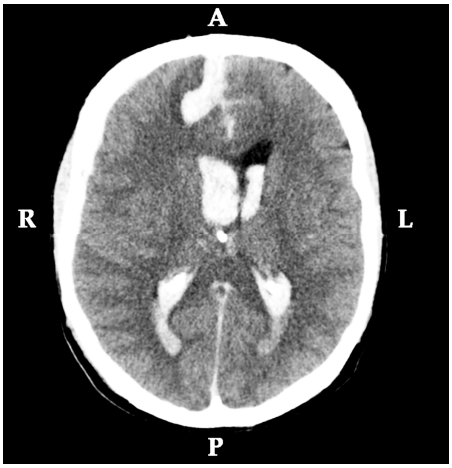

Figure 2. CT performed 24 h after admission. Note the greater amount of blood in the ventricular system and the increase of right paramedian intraparenchymal hematoma with greater vasogenic oedema adjacent. The midline is now less deviated. A: Anterior; P: Posterior; R: Right side; L: Left side.

Four days after admission, the aneurysm was embolized and, 24 h later, a new CT scan was performed. The radiologist reported that there was a right frontal subdural hematoma, which extended to the sickle of the brain; frontal and interhemispheric subarachnoid haemorrhage. The intraventricular haemorrhage, in the occipital horns, had decreased with respect to the previous study. The size of the ventricles had decreased. The radiologist also reported the existence of intraparenchymal hematomas, one in the right paramedian of frontal location with hypodense halo and another in the right frontobasal region adjacent to the previous aneurysm. The perforation at the edge of the right hemispheric convexity persisted, although it was smaller than in the previous study and the deviation from the midline was also lower (image not shown).

The last CT scan, carried out 1 month after SHA, indicated that there were bilateral parasagittal frontal hypodensities in relation to the evolving hematoma; next to them were dense dotted images, which could correspond to foci of dystrophic calcification. There was a hypodense frontal subdural right collection up to 16 mm thick. No displacement of the midline was observed and atheromatous calcifications were observed in both internal carotid arteries (images not shown).

The neurological evolution of the patient during his stay in the hospital was very slow. He remained in a coma for a month, was fed through a gastric tube and received mechanical ventilation after tracheostomy. Because of this, he suffered two bacterial pneumonias, resolved with antibiotics. In addition, the patient presented insipid diabetes treated with desmopressin and water ingestion. Two months later, the patient was discharged presenting as main sequelae: spatial and temporal disorientation, recent memory loss, disinhibition, low processing speed and difficulties in understanding. Therefore, the patient was completely dependent for the activities of daily life. No significant motor affectations existed, with the exception of a global weakness and easy fatigability, logical consequences of the process suffered and the time spent in the hospital. Insipid diabetes had disappeared and the only medication prescribed was statins for lowering plasma cholesterol and Levetiracetam 300 mg, orally (3/day) for preventing seizures.

After 8 months receiving neurorehabilitation (neurostimulation and physiotherapy) in a private centre without reaching significant improvements in his cognitive disabilities, the patient was admitted to our centre, one year after the SAH occurred.

Upon admission to the Foltra Medical Centre, the patient showed no physical disability but significant cognitive disorders, as described above. Prior to treatment with growth hormone (GH) and melatonin, routine blood tests (hematimetry and biochemistry) and hormonal analysis (plasma levels of thyroid hormones, cortisol, IGF-I and IGFBP3), as well as plasma levels were performed of some tumour markers (CEA and PSA). The same analysis was performed after 3 months under this treatment. This medical treatment was conducted in accordance with the protocols followed in our Medical Centre and in compliance with the Spanish legislation for using GH and Melatonin "off label" and the Code of Ethics of the World Medical Association (Declaration of Helsinki). Signed informed consent for using GH and melatonin was obtained from the wife of the patient (his legal representative).

Given the absence of seizures and the normal EEG records, we decided to interrupt the administration of Levetiracetam.

2.2. Neurorehabilitation 1

The neurorehabilitation consisted of daily neurostimulation, carried out by neuropsychologists, (2 h/day). Neurostimulation was focused to try to correct the cognitive deficits of the patient, observed after performing some subtests of the Wechsler Adult Intelligence Scale I (WAIS I) test and subtests of orientation of the Revised Barcelona Test (TBR).

GH and melatonin treatments started 5 days after commencing neurorehabilitation, once blood analysis indicated that there was not any contraindication for administering GH (Nutropin, Ipsen Pharma, Barcelona, Spain; 0.8 mg/day, 5 days/week, sc.), although there was no deficit of this hormone. Melatonin was prepared by master formula and was given orally, uninterruptedly, at a dose of 50 mg/day, just before going to bed.

After 3 months of treatment the patient was discharged due to family work problems and returned to his hometown. There, the patient continued rehabilitation 3 days/week. Medical treatment consisted of daily melatonin (50 mg/day) and GH (0.5 mg/day, 5 days/week) over periods of 3 months, twice per year, for two years. During that time, the patient was instructed to write down in his diary the activities that he had to do daily.

2.3. Neurorehabilitation 2

Five years later and due to the persistence of significant deficits in the cognitive sphere, especially in recent memory and processing speed and spatial and temporal orientation, the patient came back to our medical centre. On this occasion, sessions of neurostimulation, occupational therapy, auditory stimulation and sensorineural integration (EINA) and medical treatment (GH and melatonin, at the same doses indicated above) were scheduled.

2.3.1. Neurostimulation

Once examined, some items or subtests from different well-known psychological tests established the specific areas in which neurostimulation should take place. These tests were: subtests of Orientation of TBR; the D2 test, which evaluates selective attention and processing speed; the Stroop Colour and Word Test, which allows to evaluate the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus impedes the simultaneous processing of a second stimulus; the Wechsler Memory Scale for Adults (WMS-III), which evaluates the learning capacity, memory and working memory; the Complex Figure of Rey, whose objective is to evaluate the perceptual organization and visual memory in individuals with brain injury and the Wechsler Adult Intelligence Scale III (WAIS-III) to evaluate processing speed and executive functions. These tests, with the exception of TBR, were repeated in a review carried out a year and a half after discharge.

As during his first treatment period in our centre, two daily sessions of neurostimulation were scheduled, 5 days/week but now they lasted 6 months.

2.3.2. Occupational Therapy

After carrying out some occupational therapy tests the patient was scheduled for one daily session of occupational therapy (5 days/week). These tests were: Barthel scale, which evaluates the abilities of an individual for carrying out ten basic activities of daily life, therefore this test estimates the degree of functional independence; the Modified Lawton and Brody instrumental activities of daily living scale (housework, managing finances, buying groceries, cooking, planning social activities, understanding reading materials/TV, transportation, using the telephone, home repairs, bathing, dressing, shopping, laundry, taking/tracking medication, child care, work); the Functional Independence Measure and Functional Assessment Measure (FIM/FAM), which allows to measure disability in people with brain injuries; Mini Mental State Examination (MMSE), established to evaluate the cognitive status of a patient (temporal-spatial orientation, attention, concentration and memory, ability for abstraction, ability for following basic instructions and language ability and visuospatial perception); and the Lowenstein Occupational Therapy Cognitive Assessment (LOTCA), which provides a deep assessment of basic cognitive abilities and allows to be used in treatment planning and review of progress over time. These tests were repeated 3 months later and, given the advances observed in the patient, the occupational therapy sessions were then interrupted.

2.3.3. EINA

EINA is a modification, developed in our centre (for a description, see Appendix A), of the initial methods carried out by the otolaryngologist Alfred Tomatis in the 1950s to promote the internal motivation of people to listen, correct audio-vocal control and fine-tune the circuit between the ear and the voice.

First, we performed a listening test that allowed us to know how the patient perceived the sound information and to verify if the patient could isolate the sound from the environment and focus on the sound that was being sent through headphones. This test consists of several parts:

(A) Aerial listening.
(B) Selectivity.
(C) Bone listening.
(D) Spatialization errors.
(E) Laterality.

A detailed description of these items is shown in Appendix A.

After the initial listening test, two daily sessions of EINA, 5 days/week, were carried out during 3 months and 1 week. Regarding the type of music, we used different parts of sonatas by Mozart (very rich in medium and high frequencies), Gregorian chants (they have a greater number of low frequencies), Dense Music (covers the whole range of frequencies) and Pass Bands focused on stimulating a group specific frequency. These were modified in accordance with the evolution of the patient, based on listening tests and informs from other areas of therapies. In his case the sessions (45 min/day) were divided into three different blocks, differentiated by the type of music listened and the combinations among them (30 min listening to a specific music followed by 15 min listening to a different one).

(1) First block: the combinations were made between Mozart music, specific Pass Bands (to work on balance, postural control) and Gregorian chants, reaching a total of 40 sessions.
(2) Second block: consisted on 40 sessions of Mozart music, specific Pass Bands (for language, attention and memory) and Gregorian chants.
(3) Third block: consisted on 50 sessions combining Mozart music, Dense Music and Gregorian chants.

Between each block, there was a week of rest. This therapy was done for 3 months and a week.

2.3.4. Medical Treatment

Before commencing a new course of therapy with GH and melatonin, blood tests were done, as described above. After obtaining signed informed consent, GH and melatonin were prescribed in the same doses as during his first treatment period in our centre (0.8 mg/day, 5 days/week and 50 mg/day, respectively). Blood tests were repeated, measuring the same parameters than before commencing the treatment, as indicated above.

On this occasion, the total treatment period lasted six months.

A year and a half after discharged, the patient came again for a review of his evolution. Due to the improvements observed in the neuropsychological tests and his abilities to carry out an almost totally independent daily life, the patient was discharged definitively without any other treatment than melatonin (50 mg/day). Melatonin was continued because of its known neuroprotective effects.

3. Results

3.1. Neurorehabilitation 1

3.1.1. Blood Analysis

At admission, all the parameters analysed were in normal values. Plasma values of IGF-I and IGFBP3 were 182 ng/mL and 4.41 μg/mL, respectively. Three months later, at discharge, no significant changes in glycaemia existed and plasma IGF-I had increased to 221 ng/mL, while IGFP3 value was 5.3 μg/mL (both values were within the normal range for the age of the patient).

3.1.2. Neurostimulation

At admission, the patient was absolutely disoriented in the personal sphere, space and time, as the subtests of TBR revealed (scores <5 in each case, indicative of a very significant deficit). These values did not change after discharge.

The subtests of WAIS I also indicated that the typical score reached in the items analysed also indicated a clear deficit in arithmetic, similarities, digits, number key, incomplete figures, cubes and puzzles (Table 1) and although the scores reached in these subtests increased after 3 months of treatment, the improvements were quite poor, not being in any case superior to half of the lower value of the average ranges of the normal population (Table 1).

Table 1. Neuropsychology 1. Scores reached at admission (PRE, year/month/day) and at discharge 3 months later (DISCHARGE) in some items of the WAIS I test. The average range of typical scores in a normal population ranges from 30 to 70 for each of these items. Therefore, the patient continued to present very important cognitive deficits.

Date **Subtest WAIS I**	**PRE** **2010/02/14** **Typical Score**	**DISCHARGE** **2010/05/14** **Typical Score**
Arithmetic	11	12
Similarities	12	15
Digits	11	13
Number key	9	10
Incomplete figures	12	15
Cubes	10	13
Puzzles	12	15

3.2. Neurorehabilitation 2

3.2.1. Neurostimulation

When the patient came to our Centre for the second time, he remained absolutely disoriented in the personal sphere and in the spatial and temporal orientation (scores <5 in the subtests of TBR). However, his language was fluid. Interestingly, scores in the D2 test indicated that his attention clearly increased, with Pcs in the items of this test ranging between 20 and 67 (Table 2). His processing speed also had significantly increased, as revealed by Typical scores in the Stroop test, already in the normal range (30–70) for a normal population and Scalar scores in subtests of the WAIS III Scale (normal range 8–12), reaching an Index of 89 in the WAIS III scale, as shown in Table 2. However, his recent memory was still very poor, as revealed by the Scalar scores reached in subtests of the WMS-III scale, clearly below the normal range and the Pc 1 in the Complex Figure of Rey (Table 2). Despite it, executive functions were now in normal ranges (Table 2).

Given that most of these neuropsychological tests cannot be carried out again until after one year has passed since the previous ones, because they can lead to erroneous results, the patient was not evaluated at discharge but a year and a half later; however, his evolution, according to their therapists and medical doctors, was continuous and very good. After discharge, the patient no longer received any treatment, medical or rehabilitative, with the exception of his daily dose of melatonin 50 mg.

The same neuropsychological tests were performed a year and a half later. As shown in Table 2 (2017), Attention, Processing speed and Executive functions clearly improved in relation to the scores reached two years before (Table 2, 2015), not only being in the average range of the normal population but also exceeding the upper limit of this range in some of the subtests carried out. The patient was already oriented in time, space and the personal sphere. Its main problem, recent memory, had also improved significantly, although in some respects it was still below the ranges for the normal population but already very close to these or even within them (Table 2, 2017). All this allowed the patient to carry out a practically normal daily life.

Table 2. Neuropsychology 2. Scores reached in some neuropsychological tests carried out in the second admission (2015, year/month/day) and a year and a half after discharge (2017). The average range of typical scores in a normal population ranges from 30 to 70 for each of these items. The average range of Scalar scores in a normal population ranges 8 to 12. Pc = percentile. Note the marked changes between scores reached at admission in 2015 and those obtained in the same subtests when the patient was evaluated in the review carried out 2 years later. DAM = delayed auditory memory.

Tests			Date 2015/05/20	Date 2017/05/22
ATTENTION	**D2**		**Pc**	**Pc**
		TR	45	45
		TA	30	40
		O	20	20
		C	30	15
		TOT	45	45
		CON	42	49
		VAR	67	75
PROCESSING SPEED	**Stroop test of words and colors**		**Typical Score**	**Typical Score**
		P	34	26
		C	30	31
	Subtests of the WAIS III Scale		**Scalar Score**	**Scalar Score**
		Number key	9	11
		Symbol search	9	13
			Index	**Index**
		Processing speed	89	111
MEMORY	**Subtests of the WMS-III Scale**		**Scalar Score**	**Scalar Score**
		Tests I	2	9
		Couples I	3	6
		Tests II	1	7
		Couples II	1	6
		DAM	1	7
	Complex Figure of Rey		**Pc**	**Pc**
			1	5
EXECUTIVE FUNCTIONS	**Subtest cubes WAIS III**		**Scalar Score**	**Scalar Score**
			10	16
	Subtest digits WAIS III		8	12
	Subtest of letters and numbers. WMS-III		11	13
	Space location subtest. WMS-III		10	12
	Work memory index. WMS-III		**Index**	**Index**
			101	115
	Complex Figure of Rey		**Pc**	**Pc**
		Time	75	95
		Accuracy	75	95
	Stroop Interference Test		**Typical Score**	**Typical Score**
			52	59

3.2.2. Occupational Therapy

As expected, the index of Barthel was practically normal at admission, because the patient only needed some help to dress and undress correctly but this was corrected at discharge from occupational therapy 3 months after starting with it (Table 3). All the scores in the tests carried out in this area showed a clear increase at discharge, with the exception of the Modified Scale of Lawton and Brody in which the decrease observed at discharge is related to greater functional independence.

The lowest score was found in the Mini mental state, because of the poor recent memory but this was also improved at discharge, in correlation with data found in the neuropsychological sessions.

At discharge the patient was able to drive alone, although by known routes, he was able to call by phone and to manage the money, as well as to carry out housework (including cooking) and manage in his social circles, something impossible for 4 years after his stroke.

Table 3. Occupational therapy. Scores reached in different tests carried out at admission (PRE, year/month/day) and 3 months later (DISCHARGE from Occupational therapy). In each of the tests, the score obtained is accompanied by the maximum value (/) for that test. In the case of the Modified Scale of Lawton and Brody, the lower the score the higher the functionality (a score of 8 reflects maximal independence), unlike what happens with the other tests performed.

Date Test	PRE 2015/06/01 Scores	DISCHARGE 2015/09/01 Scores
BARTHEL	95/100	100/100
LAWTON and BRODY	20/31	15/31
FIM/FAM	178/210	192/210
MINI MENTAL STATE	20/37	28/37
LOTCA	80/87	85/87

3.2.3. EINA

At admission, the patient showed an important abnormality for his age in the listening threshold for treble frequencies (3000–8000 Hz) of the aerial way, especially in the right ear (Figure 3, Test 1). There was also an inversion of the curves for aerial and bone listening (red curve over the blue curve (Figure 3, Test 1), which was also more marked in the right ear. Moreover, there was no symmetry in the listening curves between both ears. At discharge from this area of therapy, there was a better symmetry between the listening curves corresponding to the vestibular area (0–1000 Hz) and the area of language (1000–3000 Hz) between the two ears (Figure 3, Test 2). A large part of the inversion of curves has been corrected, although the improvement was greater in the left ear. Regarding the listening thresholds, although in some areas they had decreased slightly, the important thing is that the functionality was improved when correcting the inversion of curves because this allows the information to be transmitted and processed better from the middle ear to the corresponding cerebral hemisphere. It also significantly improved the area related to the cognitive part (3000–8000 Hz) in the right hemisphere (Figure 3, Test 2, left ear).

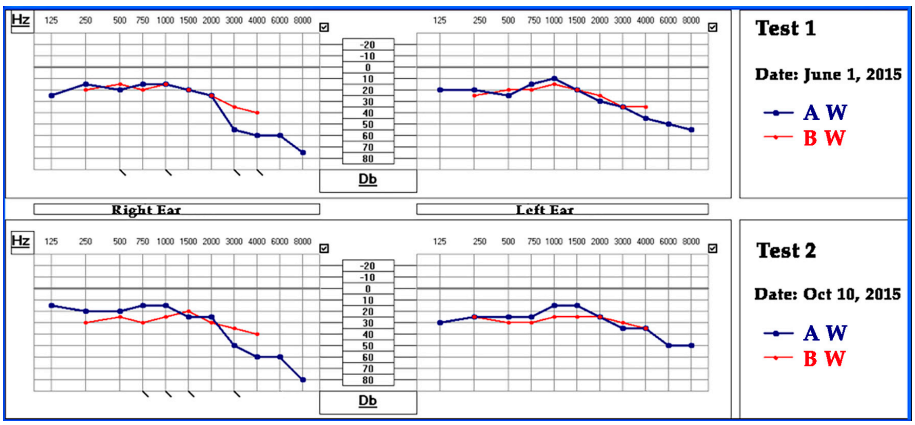

Figure 3. EINA. Listening tests performed at admission (Test 1) and at discharge in this therapy (Test 2). In Test 1 the Bone Way (red curve, B W) of sound transmission overlapped the Aerial Way (blue curve, A W) at frequencies up to 2000 Hz or exceeded it from these (3000 Hz), while in Test 2 the B W was practically normal while listening to low frequencies, especially in the right ear, although it persisted an abnormality in treble frequencies in this right ear. Note that in this ear there were some mistakes of spatialization in both Tests (indicated by marks on the abscissa axis), indicating that the sound is being analysed by the opposite hemisphere to the one that corresponds to it; these were not observed in the left ear. No significant changes were observed in the threshold of listening in the right ear, while a gain of 5 Db appeared in the left ear at frequencies between 3000 and 8000 Hz, which are related to cognition.

3.2.4. Blood Analysis

Blood analysis showed that no significant changes occurred in the parameters analysed during the treatment and the end of it. Maximal glycaemia value was 97 ng/mL; plasma IGF-I reached a maximal value of 296 ng/mL (normal for his age), while that of IGFBP3 was 5.8 µg/mL (also in normal ranges). Tumoural markers continued to be in normal ranges and no secondary adverse effects were observed after GH and melatonin administration.

4. Discussion

One of the main problems occurring after a SAH is the appearance of cerebral ischemia. This is because soon after the bleeding an important vasoconstriction occurs in cerebral arteries, perhaps as a mechanism of defence against bleeding. Following this vasoconstriction, a delayed vasospasm appears, usually more than 48 h after that, as pioneering studies in rats revealed [29,30]. Many theories have tried to explain how this delayed vasospasm occurs, among them an alteration in the production of nitric oxide (NO) by the vascular endothelium [31], hence impairing the vasodilatory activity of this gas and the hemodynamic cerebral autoregulation. Following haemorrhage haemoglobin binds to NO, therefore decreasing its availability [32]. The consequence is that NO-activated guanylate cyclase (GC), which produces cyclic guanosine monophosphate (cGMP) responsible for the activation of intracellular pumps that sequester free Ca^{2+} into sarcoplasmic reticulum producing relaxation of vascular smooth cells [33], does not act and then vasoconstriction occurs.

In the case of the patient here described, nimodipine infusion was used for treating or preventing vasospasm. However, the severity of the bleeding he suffered produced in him very important sequels in the cognitive area.

As described, we began to treat the patient with GH and melatonin, besides specific neurostimulation. We used GH, although there was no deficit of the hormone, because of its well-known effects on brain repair after an injury [23–27]. In fact, one of us (JD) was the first (December 2002) in using GH to treat early a young man with a diffuse axonal injury, traumatic SHA and brainstem affectation, whose vital future was unpredictable. Despite the severity of brain injuries suffered, eight months after his traffic accident, he came back to his University studies and normal life. We published this case 11 years later ([26] see Case 1).

GH plays a key role in neural development [34] and also exerts important neuroprotective and neuroregenerative effects [24,26,27,34–37]. Particularly, the hormone plays a significant role at the cognitive level [25–27,38–44], even in the case that no GH-deficiency exists. Moreover, GH is an inducer of endothelial production of the vasodilator NO and recovers endothelial dysfunction [6,37,45]. Therefore, this hormone might be of utility in the prevention of the cascade of deleterious effects subsequent to SAH but also to recover the arteries most likely damaged in the case of our patient.

GH crosses the blood-brain barrier (BBB) and GH-receptors (GHR) are widely distributed in the Central Nervous System, mainly in the choroid plexus and hippocampus [38]; while the former seems to be used for the transport of the hormone across the BBB, hippocampal GHR are involved in the effects of the hormone on memory and cognitive functions. In fact, we described that GH and GHR are expressed in neural progenitor cells in the dentate gyrus of the hippocampus, in rats, where they increase the proliferation of these neural progenitors in response to a damage induced by kainic acid [46]. Moreover, in that study we also demonstrated that exogenous GH cooperates with the hormone produced in the neural progenitors to increase their proliferation in response to a brain damage. The effects of GH treatment on the proliferation of neural stem cells, had been also observed in adult mice and rats [47,48] and human foetal hippocampus [49]. Moreover, a functional MRI study demonstrated that GH treatment improved learning and the working memory in GH-deficient GHD) children [40,42]. This agrees with data indicating that GHD-adults show cognitive deficits, particularly attentional deficits and altered processing speed [39], as well as with the first description of that local synthesis of GH takes place in the hippocampus in response to a memory task [34] and to the fact that higher levels of circulating GH are related with a better working memory in non GHD adults [43].

Therefore and despite the patient that we describe here had to be treated intermittently with GH and neurostimulation, because of the reasons stated above and the long time elapsed since he suffered his brain damage, it seems to be clear that it was the GH treatment the factor mainly responsible for his recovery. A support to this affirmation comes from the results obtained in a 10-year-old girl, non GHD, who presented important cognitive deficits (among them absolute absence of memory), because of a neonatal asphyxia. Nine months of treatment with GH and neurostimulation resulted in a complete recovery of her cognitive deficits [44].

At this point we cannot forget the role played by melatonin and neurostimulation, including the specific EINA method.

In the case of melatonin, its multiple beneficious actions have already been widely described in the scientific literature, including its role as a neuroprotective hormone because of its direct and indirect antioxidant and anti-inflammatory roles [50]. Even, a recent study demonstrates that melatonin induces neuroprotective effects in animal models of SHA and intracerebral haemorrhage, proposing that the administration of this hormone might be useful for therapeutic applications in haemorrhagic stroke [51]. Given the clinical antecedents of the patient and the absence of secondary effects of melatonin, we decided to treat him with this indole-amine continuously after his first admission in our Centre.

In relation to neurostimulation, it is necessary to analyse the effects induced by the EINA method. Music is a multisensorial stimulus that leads to the activation of many brain areas related to sensory processing, including attention and memory and can enhance multisensory integration [52]. It has been proven that daily listening to selected music may improve verbal memory and attention after stroke, enhancing cognitive recovery [53]. This was first postulated in 1993, indicating that listening to specific Mozart sonatas (the so-called Mozart effect) had a positive effect on learning [54] but this hypothesis was controversial for many years, although the effect of Mozart music in rehabilitation has been demonstrated in many studies [55]. In our patient, a clear gain was observed in the left ear after three blocks of EINA, in frequencies related to cognition (3000–8000 Hz), which is consistent with the results observed in the cognitive tests carried out at discharge from his second admission and when he was reanalysed two years later. Moreover, although our EINA method is a modification of the former Tomatis effect, some recent publications describe the influence of Mozart's sonatas, particularly the sonata K448, on brain activity evaluated by EEG. One of them, carried out in young healthy adults, healthy elderly and old people with mild cognitive affectations, showed that after listening to Mozart' sonata K448, an increase of alpha band and median frequency of index of background alpha rhythm activity was observed in the former two groups analysed. These EEG waves are linked to memory, cognition and processing speed to solving problems; however, no EEG changes were observed in the same populations after listening to "Fur Elise" sonata by Beethoven. The authors conclude that this Mozart's music activates by unknown mechanisms neuronal circuits related to attention and cognition [56]. A further support to this Mozart effect on the brain, comes from recent studies demonstrating that listening to this sonata K448 decreases the number and severity of drug-refractory epileptic encephalopathies in children and young adults [57–59].

In summary, we demonstrated here that cognitive functions lost after an important SAH can be recovered with a treatment combining GH and melatonin administration and specific neurostimulation. Most likely, if we had been able to treat this patient earlier and without interruptions, the positive results would have been reached sooner; but in any case, our data indicate that there is not a plateau for reaching significant improvements after a brain injury. Moreover, short-term treatments with GH are useful and safe, as we demonstrated previously, even in the case that the patient is not GH-deficient [6,26,27,60]. In addition, although GH replacement therapy has been related to the related to the future development of stroke [61], more recent studies rule out this possibility [62,63].

5. Conclusions

GH and melatonin administration can be useful tools for facilitating the recovery of a patient who suffered a subarachnoidal haemorrhage. During the post-acute period these hormones also improve the lost cognitive functions; specific neurostimulation, including EINA, is of great help for enhancing the neuroregenerative effects of GH and facilitating the creation of new neuronal circuits that would replace the lost ones after the SAH, perhaps because facilitating brain plasticity, as we recently demonstrated in rats treated with GH after a severe frontal motor cortex ablation [36,64].

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Author Contributions: Ana Quintana and Carlos Agra carried out neurostimulation and interpreted the results of the neuropsychological tests. Lucía Outeiral was responsible for occupational therapy, treatment and evaluation of the tests. Ana Devesa and David Llorente designed the different blocks carried out in EINA and interpreted the results obtained. Jesús Devesa designed the medical treatment and neurorehabilitation that the patient had to receive and wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

EINA

In our case, we utilized:

(A) An electronic ear in which we can vary and control the sound characteristics of channel 1 and channel 2 (treble and bass frequencies, from +5 to −5 Hz, in both cases); the delay (a neurological parameter; is the time that an ear needs to listen or the time of preparation to receive the acoustic information. The electronic ear gives us the possibility of establishing a lapse of time between the moment in which the sound threshold is reached for the scale to pass from channel 1 to channel 2 and the moment in which that step actually occurs); the precession, is the advance or the advantage that bone conduction takes over air conduction. First the bone conduction passes to channel 2 and then the aerial conduction (in the electronic ear this is reflected by the introduction of a time lapse that shifts the passage from channel 1 to channel 2 of the aerial conduction with respect to the passage of bone conduction. In practice, with precession 10, the phase shift is 250 ms and with precession 100 the phase shift is 2.5 s); Sound filtering—the electronic ear is equipped with a filter that allows it to eliminate the lower frequencies as appropriate, or add them depending on the desired programming; bone volume—the volume that is given to the vibrator.

In the listening test, it would be the decibels (Db) to which the patient listens to of a certain frequency through the vibrator, while in the programming of the electronic ear it would be the Db to which a certain frequency would be emitted in the vibrator of the headphones; air volume—the one that is given to the headphones. In the listening test, it would be the Db to which a certain frequency is heard by the headphones (via middle ear). In the programming of the electronic ear would be the volume of the headphones; balance (different volume in each headphone). In order for the electronic ear to lateralize a person's hearing, it is possible to send the sound signal identically to the two headphones or to reduce the sound power in the left ear from 100% to 10% by steps of 10%.

(B) Equalizer and pass bands, to stimulate or not stimulate certain frequencies; we use the equalizer (Tomatis' method does not use it) and recorded music with pass bands. This is based on the pre-listening test. For example, if a person listens to frequencies (Hz) in values of, for example, 10–15 Db and others in values of 50 Db, if we put out a general stimulation volume of 45 Db, at the frequencies that the patient starts listening to 50 Db are not heard and therefore they do not stimulate. If we raise the volume the patient can feel discomfort in the frequencies that he hears at lower Db and that is why it is necessary to equalize, give a different volume of sound at each frequency. If a patient is hypersensitive at certain frequencies the volume must be decreased by negatively equalizing so that they do not "bother" and stimulation does not produce a negative effect. In relation to the

passing bands, they are groups of sounds of certain frequencies. They are recordings that have those frequencies equalized in positive, with more volume. We use vestibular passive bands (from 0 to 1000 Hz) to enhance functions in which vestibular control intervenes (balance, coordination, postural control, rhythm, etc.); passages related to language (1000 to 3000 Hz), to improve both the perception of those sounds as the control in the emission of voice. (C) We use analogue sound, instead of MP3 or cut out or compressed sounds. (D) In some types of patients, we use water mattress while listening to EINA.

Regarding the listening test, it is necessary to clarify that it is not an ordinary audiometry since the patient is not isolated from the environment. This test consists of: (A) Aerial listening: with headphones, we can see what volume the patient listens to each frequency at (from treble to bass) even if he/she perceives it to be very low. First in the right ear and then in the left; (B) Selectivity: through the same headphones we emit different frequencies to be compared two by two. The patient must differentiate which of the two is more acute. It is done with all frequencies from treble to bass, first in one ear and then in the other. If the patient is able to differentiate all of them, selectivity is open. It is not normal that the selectivity is closed after 10 years of age; (C) Bone listening: a vibrator is placed behind the ear of the patient so the sound is transmitted directly to the inner ear. As in the aerial listening, we will observe to what volume each frequency is perceived. First in one ear and then in the other; (D) Spatialization errors: is done in conjunction with the previous test. When the patient tells us when he begins to perceive the sound emitted through the vibrator, he should also tell us if he hears it on the right side, on the left side or on both. If it says on the opposite side to the one we are stimulating, it means that there is an error of spatialization, so the sound is being analysed by the hemisphere opposite to that which corresponds to it. (E) Laterality: allows to know if the patient listens better by one ear than by the other, although it can also be the case that there is no auditory dominance. This test cannot be performed if there is facial paralysis or paresis.

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