Case Report

Multidisciplinary Care in Unknown Dopaminergic Disorder: A Case Report

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Abstract

This clinical case shows a child suffering from a dystonic-dyskinetic Dopar- responsive syndrome, of non-determined etiology, in which errors of metabolism affect the dopamine biosynthesis. This clinical picture leads to a progressive neurological deterioration, lack of postural development, rigidity and tremors, impacting very seriously on the functioning level of the child and on the family resources. Levodopa/carbidopa intestinal gel therapy is a possible treatment for motor control in Parkinson’s disease; it is delivered through a gastrostomy in the duodenum by an infusion pump, and it is unaffected by gastric emptying. After the onset of this therapy, the child achieved a gradual recovery of the postural tone and upper limbs function, succeeding to grasp and move objects. Today the child requires a high caring load by the family, which is fully absorbed during day and night. In view of supporting the clinical condition of the child, continuous home care and health professionals were required. Health professionals involved in this multidisciplinary team included home nurses, a physiotherapist, a speech therapist, a developmental neuro and psychomotor therapist, and a nursing assistant. To guarantee continuity of care, working agreement between health professionals is essential; at this regard, the nurse plays a key role. To date, clinical investigations are ongoing to define the etiological picture presented by the child and further researches are necessary to identify new strategies in delivering the best care to subjects affected from this clinical condition.

VABBREVIATIONS

CSF: Cerebrospinal Fluid; HVA: Homovanillic Acid; PROM: Premature Rupture Of Membranes; PTH: Parathyroid Hormone; NMR: Nuclear Magnetic Resonance; FISH: Fluorescence In Situ Hybridization; Array-CGH: Array - Comparative Genomic Hybridization; TH: Tyrosine Hydroxylase; GCH1: Guanosine Triphosphate Cyclohydrolase 1; GFRP: Guanosintrifosfato cyclohydrolase 1 Feedback Regulatory Protein; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; MECP2: Methyl 5’—Cytosine —Phosphate—Guanine —3’ binding protein 2; T1: Spin-lattice Relaxation; T2: Spin-Spin Relaxation; FLAIR: Fluid-Attenuated Inversion Recovery; TOF3D: Three-Dimensional Time-of-Flight; LCIG: levodopa/Carbidopa Intestinal Gel; QoL: Quality of Life; PD: Parkinson’s Disease

INTRODUCTION

As defined by Pons, infantile parkinsonism-dystonia has long been recognised as a presentation of inborn errors of metabolism affecting the dopamine biosynthetic pathway [1]. Among the most distinctive clinical features of dopamine transporter deficiency syndrome are eye movement abnormalities [2-5]. The dysregulation of dopaminergic neurotransmission probably has an important role in disease pathogenesis [2]. Kurian and colleagues’ study will most definitely spur increased use of Cerebrospinal Fluid (CSF) neurotransmitter analyses as part of diagnostic investigations in infants and toddlers with parkinsonism-dystonia. The dopamine metabolite Homovanillic acid (HVA) is usually decreased in the CSF, indicating decreased dopamine production [4]. This is a clinical case that describes the condition of a child suffering from a dystonic-dyskinetic Dopar-responsive syndrome, with nature not determined, in which errors of metabolism affecting the dopamine biosynthesis.

CASE PRESENTATION

A 4-month-old male infant presented to the paediatric ward with his parents due to slight hypo tonus at upper limbs with tremors and myoclonus. The infant was born after a second full-term pregnancy (the first with a caesarean section) in a dystocial spontaneous vaginal delivery with premature rupture of membranes (PROM), and normal anthropometric
parameters; his weight was 3.28 kg, his length was 51 cm and his head circumference was 35.7 cm. The 1-minute Apgar score was 4, the 5-minutes was 8. He had jaundice in fifth day, so he was treated with phototherapy. Akinesia and Parkinsonism of unknown aetiology was the worsening frame work that began at about eight months of this child’s life. The framework presented leads to a progressive neurological deterioration, lack of postural motor development, hypokininesia, rigidity, tremor and dystonia of the four limbs. From the age of 8 months, a slow and progressive regression of motor development occurred, whose first sign was the occurrence of axial hypo tonus. In the same period the tremors in the upper extremities intensified, and a gradual loss of babbling appeared.

In the past, the child’s mother suffered from thyroid nodules and thyroiditis, and acute lymphoblastic leukaemia at age 14; she was treated with chemotherapy and radiotherapy. The child’s father suffers from allergic asthma due to dust mite. The child’s brother had two episodes of febrile convulsions. His paternal grandfather had myocardial acute infarction at age 60.

**Neurological examination**

In May 2007 (four months old) the child showed good environmental interaction, normal visual tracking, muscle tone slightly asymmetrical because of the right upper limb had less spontaneous motor activity than the left one, closed fists hands, normal deep tendon reflexes and no obvious alteration of body morphology. In December 2007 (eleven months old) he showed a reduction of muscle tone in lower limbs with reduced evocable osteotendinous reflexes, a prevalent grasping dependent of both his right and left hand. Central and side parachute reflexes were current and valid. There were present muscle twitches with intermediate characteristics between coarse tremors and myoclonus during attention stimuli and during the execution of movements (Figure 1A). Muscle twitches were both at lower limbs (including toes), both upper limbs, and a dystonic attitude was present; when he was prone, the baby was able to assume the quadruped position, but there was fall of tone about the trunk (Figure 1B).

**Electroencephalogram**

In December 2007 (eleven months old) sharp potentials at sucking movements were showed; while recording, the child had clonic movements of lower limbs at which the pace did not change. The track appeared, therefore, without paroxysmal abnormalities. In May 2012 (five years old) synchronous and asynchronous wide theta and delta potentials at medium - high voltage were noted, having rapid widespread activity, physiological underrepresented figures, abundant spikes, sharp waves and atypical plurifocal P-O complex prevalent in anterior right regions; a critical episode with eyes deviation and left arm clonus was reported, with a long sequence of spikes, sharp waves and atypical P-O complex trend with frontal right starting and subsequent spread. The basic layout was well organized for age, but very active and plurifocal paroxysmal abnormalities were present.

**Parathyroid Hormone (PTH)**

In December 2007 (eleven months old) a slight reduction in levels of PTH occurred. One month later tests were repeated, showing lower levels. Next month levels reached range normalization (Figure 2).

**Neck Ultrasound**

In January 2008 (one year old), a normal thyroid, a hypoechic formation of 20x10 mm below the left thyroid lobe due to a thymic hypertrophy, and a hypoechic formation of 25x12 mm, of unclear definition, forward of the right carotid artery were highlighted. Eleven days after, the same picture was confirmed in a later ultrasound.

**Electrocardiogram, Echocardiogram and Eye Examination**

They were performed in January 2008, resulting normal.

**Nuclear Magnetic Resonance (NMR)**

In February 2008 (one year old) a clinical worsening due to more continuous intensification of tremors, and hypotonus, which changed from axial to generalized, occurred. The child was admitted to a pediatric clinic where the NMR resulted normal.

**Genetic counselling**

In March 2008 (one year old) were performed the following molecular studies:

- Standard karyotype was normal;

**Figure 1 Illustrations showing muscle control: (A) closed fists hands, with difficulty in reaching the target (attentional stimuli) due to intermediate muscle twitches; (B) muscle twitches also in lower limbs (clenched toes and fists) and trunk supported by braces; (C) hands no longer fisted and greater muscle control, with better achievement of the targets.**

**Figure 2 Parathyroid Hormone (PTH) levels (g/ml) - normal values range 12-72(g/ml).**
• FISH for 22q 11.2 (Fluorescence in situ hybridization on the long arm of chromosome 22 on the band of section 11.2) for suspected Di George Syndrome resulted negative;
• FISH for 7q 11:23 (Fluorescence in situ hybridization on the long arm of chromosome 7 on the band of section 11:23) for suspected Williams Syndrome resulted negative.

In April 2008 (one year old) an Array-CGH showed micro deletions and micro duplications having pathological significance, while TH and GCH1 genes showed normal results.

In November 2010 (three years old) genes encoding for the sepiapterin-reductase and phospho-tyrosine-phosphatase (phospho-tyrosine-phosphatase is involved in disorders of amino acids metabolism and transport) did not show mutations. Mutations in the gene coding for GFRP were excluded (antibody A-B is a monoclonal IgG1 provided at 200 mg/ml). Also other conditions were excluded, such as:

- Lesch-Nyan syndrome (uricuria of 24 hours and activity of hypoxanthine-guanine phosphoribosyl transferase enzyme, involved in rescue of DNA/RNA purine bases, were normal);
- Niemann Pick type C (filipin test, based on reaction of unesterified cholesterol with fluorescent antibiotic filipin giving a strongly fluorescent, stable cholesterol-filipin complex suitable for in situ detection, resulted normal);
- Ceroid lipofuscinosis type 1 and 2 (was normal);
- Rett syndrome (absence of mutations in MECP2 gene).

Blood and Urine tests

In April 2008 (one year old) acanthocytes peripheral smear, urine catecholamine, prolactin, asylcarmitines, plasma amino acids, urine organic acids, and blood lactate, ammonia, hexosaminidase A, B and total betagalactosidase, beta-galactosidase, alpha-iduronidase, isoelctrofocusing of sialotransferrine, semi-quantitative protein ataxia-telangiectasia mutated and aprataxin, vitamin B12, A, E and folate were carried out. All these exams were normal. In November 2010 (three years old) the child was subjected to following tests: creatine and creatinine, semi-quantitative protein ataxia-telangiectasia mutated and aprataxin, vitamin B12, A, E and folate were carried out. All these exams resulted in the normal range. In November 2010 (three years old) a marked reduction in HVA and neopterin was confirmed (Table 1).

Drug Treatment

In April 2008 (one year old), after evaluating results of lumbar puncture, the inclusion of levodopa in the treatment had been recommended. In May 2008, levodopa/carbidopa intestinal gel (LCIG) 50/12.5 mg/day was included, followed by an improvement of the anti gravity tone and a reduction of dyskinesias. In October 2008 (one year old), LCIG was increased to 100/25 mg/day. In February 2009 (two years old), for lower levels of parathyroid hormone, calcium supplementation had been prescribed; after starting therapy an improvement of the clinical picture had been showed. Until November 2010 (three years old), the response to drug therapy appeared good, with no evidence of significant side effects (Figure 1C); after that, significant diurnal fluctuations in the efficacy of the therapy were reported; the child did not respond to treatment as expected; side effects appeared, such as dyskinesia, distal tremor, myoclonus and accentuation of dystonic attitudes. In the morning, before LCIG, there was complete absence of antigravity tone and there was hypomotility, due to neurotransmitter depletion. Instead, after LCIG administration, the child had gradual recovery of postural tone, used upper limbs, could grasp and move small objects, and showed greater participation in its environment, being more present and involved, but, at the same time, dyskinesia increased. During the day, on-off phenomena (the

<table>
<thead>
<tr>
<th>Date</th>
<th>Age</th>
<th>CSF HVA nmol/l</th>
<th>CSF Neopterin nmol/l</th>
<th>CSF Bioterin nmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apr</td>
<td>One year old</td>
<td>185.5 (295-932)</td>
<td>7.8 (12-30)</td>
<td>5.5 (15-40)</td>
</tr>
<tr>
<td>Nov</td>
<td>Three years old</td>
<td>77 (231-840)</td>
<td>1.84 (2.30-7.60)</td>
<td>-</td>
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</tbody>
</table>

Magnetic resonance brain imaging

In May 2008 (one year old), no pathological changes had been showed. In May 2012 (five years old) T1, T2, FLAIR and TOF3D weighted multi planar sequences for the study of intracranial arterial circulation were performed; alterations of signal intensity were not detected, nor pathological impregnation after administration of contrast medium, in intra- and extra-axial site. No cortical changes or migration defects were present. An enlargement of supra tentorial ventricular system was shown, which resulted in axis with respect to the median line. The morphology of callosum corpus, fourth ventricle and coat subarachnoid space were normal. Instead, there were changes in the spectroscopic graph performed at right semi-oval centre.

Lumbar Puncture

In April 2008 (one year old) a reduction in Homovanillic acid (HVA), neopterin and bioterin was shown (Table 1). In the same period CSF lactate, CSF chemistry, galactocercerobiosidase, relationship glucose/CSF serum, amines biogenic, pterins, CSF folate, purine and pyrimidine metabolites were carried out. All these exams resulted in the normal range. In November 2010 (three years old) a marked reduction in HVA and neopterin was confirmed (Table 1).

Visually Evoked and Cerebral Potentials

In April 2008 (one year old) both these exams were normal. In May 2012 (five years old) the right eye pattern showed large angular, with amplitude response in the range and increased latency. The flash of the right eye showed the P2component with amplitude and latency in the range. The left eye pattern showed large angular, with amplitude response in the range and increased latency. The flash of the left eye showed the P2component with amplitude and increased latency. Among the most distinctive clinical features of dopamine transporter deficiency syndrome are eye movement abnormalities [2-5].
phases in which the therapy has, respectively, a positive effect and not) were shown, whereby a hypokinetic-apostural picture was followed by dystonic attitude, tremors, and myoclonus at limbs, with widespread stiffness.

**DISCUSSION**

This case study raises some questions:

1. **What tools are capable of improving the quality of life (QoL) of the child?**

The non-motor fluctuations often influence the quality of life (QoL) in a much more negative way compared with the motor symptoms [6]. The child requires a high caring load by the family, which is fully absorbed during day and night. In the few hours of efficacy of LCIG, the child can control the head and trunk, has a valid swallowing and good level of environmental participation. Outside the hours of drug efficacy, severe dysarthria with an almost total inability to carry out aimed actions is shown. In general, despite the movement disorder, the child is able to communicate through the use of gaze, gestures and vocalization/guttural sounds and he is able to understand verbal communication.

**Infusion Pump:** The continuous LCIG infusion is a valid alternative for motor control in advanced Parkinson’s disease (PD). An improving motor fluctuation with a global increase in “on” phase has been demonstrated, generally without the outbreak of troublesome hyperkinesia [7]. For the child is extremely difficult continuing school cycle, due to sudden fluctuations in relation to the effect of drugs. As for difficulties in postural positioning, there are not, unfortunately, suitable aids to facilitate the sitting position during the “on” and “off” phases. In September 2014 (seven years old) the child undergone surgery for implantation of a infusion pump (Figure 3) in order to administer levodopa-carbidopa intestinal gel and favour greater prosperity and cooperation in carrying out some daily activities (mainly eating and gaming). Levodopa-carbidopa infusion pump brings the child to maintain a new posture in a padded wheelchair, with adjustable seating system (Figure 4); this improvement allows the child to communicate and control the activation of inputs for the use of computer aids or low technology tools. Improvements in overall clinical condition, such as motor skills, attention and participation, allows the child to experience for a long time (more than the maintenance of phase “on”) a series of activities based on: (a) communication through the use of gaze, (b) communicative stimuli both towards stakeholders, both on electronic technologies for communication, play and learning, and (c) confirmation of cognitive potential, in an active participation in the context and situation, even in the conduct of activities.

2. **What is the proposed multidisciplinary management for this patient?**

In order to supporting the clinical condition of the child, continuous home care and health professionals were required (Table 2). Health professionals involved in this multidisciplinary team included home nurses, a physiotherapist, a speech therapist, a developmental neuro and psychomotor therapist, and a nursing assistant. To guarantee continuity of care, working agreement between health professionals is essential; at this regard the nurse plays a key role as case manager. Furthermore the nurse reports fluctuations in response to medication when observed.

**Stoma care:** LCIG is delivered continuously through a percutaneous endoscopic gastrostomy with the inner tube placed in the duodenum by an infusion pump. The therapy implies continuous dopaminergic delivery directly to the duodenum and it is therefore unaffected by gastric emptying [8]. LCIG has a short plasma half-life of approximately 90 minutes; and it is rapidly metabolized [9]. The stoma encountered complications such as secretion and formation of hypertrophic granulation tissue. Local
3. How can the caring needs of this child be assessed?

Nursing Care: In this clinical case, characterized by high complexity of care, nurses have an important role in ensuring the continuity of care, in order to improve the quality of life of the child and his family. For this reason, nurses are requested both to coordinate as a case manager the other health professionals involved in the care process, and to be experienced vigilant caregivers in ensuring the little patient's safety in his family setting [10]. In order to a better needs assessment of the child, the eleven Marjory Gordon’s Functional health patterns were used (Table 3). The structure of functional health patterns allows an orderly data collection in order to prevent the omission of information, so that next phase of the nursing process, that is the definition of nursing diagnosis, can be developed. In Table 3 are also shown some nursing diagnoses. For example, an important nursing diagnosis is “Risk for infection due to presence of the stoma” whose outcome is the “absence of infection”. At this regard, the nurse has the ability to weigh and minimize risk, which is a characteristic of professional vigilance mentioned above. In addition to the direct interventions performed on the stoma; the nurse has to perform the educational ones to the child and his family. For this reason, nurses are requested both to coordinate as a case manager the other health professionals involved in the care process, and to be experienced vigilant caregivers in ensuring the little patient’s safety in his family setting [10].

### Table 3: Data assessment based on Gordon’s functional health patterns and some related nursing diagnoses.

<table>
<thead>
<tr>
<th>Model</th>
<th>Data</th>
<th>Nursing Diagnosis</th>
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| Health Perception & Management| 8 years-old. He shows disease awareness and willingness to perform medical and nursing prescriptions. | - Risk for Chronic Low Self-Esteem  
- Risk for infection due to presence of the stoma |
| Nutritional-Metabolic         | Dependent feeding. Moderate orthodoxy and paradoxical dysphagia. Increased appetite. Percutaneous endoscopic gastrostomy (PEG) for food and drug (Duodopa). Taking two glasses of water a day. Presence of risk factors for impaired skin integrity. | - Risk of aspiration due to impaired swallowing  
- Risk for impaired skin integrity |
| Elimination                   | Frequency of bowel elimination 2-3 times a day. Absence of urinary retention (2-3 times a day). | - Bowel incontinence |
| Activity - Exercise           | General functional mobility altered (myoclonus, ophistotonus and tremors). Muscle tone altered (muscle hypotonia and hypoplasia). Cough. Use of aids and assistance / supervision of a caregiver required for daily life activities (DLA) (food, hygiene, bathing, toilet, dressing, appearance, walk, bed mobility). | - Impaired mobility  
- Impaired self-care |
| Sleep Rest                    | Night sleep from 1:00 to 10:30. Sleep during the day altered. Night-time awakenings. Perception of well-being after PEG insertion to administer levodopa/carbidopa intestinal gel (LCIG). | - Disturbed sleep pattern |
| Cognitive-Perceptual          | Hearing, sight, smell, taste and feel are normal. Good understanding and comprehension of language. Difficulty of words articulation, sounds emission only. Attention and concentration disorders. Anxiety. | - Impaired verbal communication |
| Self Perception/ Self Concept | Perception of cognitive and affective skills. Body image disorder. | - Anxiety  
- Disturbed body image |
| Role-Relationship             | Life in family. Functional reaction to the disease by the family. Loss of mastery of the role. Social life is absent. Correct model of interaction with health care professionals, but sometimes the child becomes estranged. | - Impaired social interaction |
| Sexuality                     | Nothing to detect currently. | - |
| Coping-Stress Tolerance       | Functional adaptability skill to situations. Presence of support systems (family and health care professionals). Sources of stress / life changes in the last year. | - Readiness for enhanced family coping |

secretion and inflammation around the stoma was treated with silver-based gauzes. The nurse has to ensure that the catheter may become blocked or kinked. Nurse can eliminate the blockage by flushing the catheter with water, and can eliminate kinks by straightening the catheter.

**Passive exercise:** Since the child is subjected to continuous muscle contractions, the passive exercise performed by the physiotherapist has focused on extending muscle and hiking joints.

**Speech-Language Therapy:** It is based on two issues: (a) difficulty with speech, focusing on intensive stimulation of the spech, the voice, the intelligibility, finding words and starting a conversation; (b) difficulty with chewing, swallowing and difficulty with controlling saliva, focusing on providing adequate myofunctional tongue exercises and movement strategies.

**Communication strategies:** There is a need of an improvement of the postural system, since the currently postural system used by the child is not totally suited to the current clinical condition. In addition to the postural system, the child should be put in a favourable position to use augmentative communication systems.

**CONCLUSION**

This clinical case shows a child affected by a dystonic-dyskineticDopa-responsive syndrome, of not determined etiology, in which errors of metabolism affect the dopamine biosynthesis. This clinical picture leads to a progressive
neurological deterioration, lack of postural development, rigidity, and tremors, impacting very seriously on the functioning level of the child and on the resources of the family. LCIG therapy is an alternative for motor control in Parkinson’s disease; it is delivered through a gastrostomy in the duodenum by an infusion pump, and it is unaffected by gastric emptying. After LCIG administration, the child had gradual recovery of postural tone, upper limbs, grasping and moving objects. A multidisciplinary team is desirable in order to manage the treatment, the caring and optimize daily performance as described in this case study. To guarantee continuity of care, working agreement between health professionals is essential, and at this regard the nurse plays a key role. To date, clinical investigations are ongoing to arrive at a definition of the etiological picture presented by the child and further researches are necessary to identify new strategies in delivering the best care to subjects affected from this clinical condition.

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REFERENCES


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