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Unpredicted failure of deep brain stimulation by the impedance measures in a child with severe *PANK2*- gene related generalized dystonia



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DYT-PANK2
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1. Introduction

Deep brain stimulation (DBS) therapy is exploratory in pediatric dystonia related to progressive, degenerative disorders with ethical issues together with benefit to risk ratio for a given child to be considered. *PANK2* gene mutations are responsible of pediatric onset complex, severe generalized dystonia. Despite recent physio-pathological based approaches with iron chelation [1,2], there are no approved efficient available therapies for pantothenate kinase-associated neurodegeneration (PKAN) leading to lasting symptom improvement and stabilization of disease progression. DBS remains the most reported useful therapy in alleviating severe dystonia in PKAN [3]. DBS interruption may relate to DBS system failure and be responsible for severe dystonic crisis [4].

Here we report on a child who presented, nine months following initial DBS surgery with bilateral extension cable fracture, *without* documentation of consecutive DBS system impedance abnormalities, leading to delayed surgical replacement and consequently, to 'pre-status dystonicus' [5].

2. Case report

An 8-year-old female with PKAN came to our attention because of worsening dystonia. Delay in achievement of milestones and learning impairment were followed by onset of dystonia and swallowing difficulties at 5 years of age. She was admitted to local hospital because of rapid symptom progression with medication refractory frequent opisthotonic spasms and transferred to our neurosurgery department for bilateral globus pallidus internus (GPi) DBS. Stimulation was administered on Boston Scientific Verise Gevia system, in monopolar ring mode bilaterally with the segmented level 2 (contacts 2, 3 and 4), followed by progressive clinical improvement with suppression of opisthotonic spasms and dystonia involving upper extremities; the child was more comfortable, able to sit, to help during transfer and could eat

autonomously. Deferiprone [1] was initiated three months post-DBS but discontinued because of digestive adverse events. DBS settings were adjusted six months post-DBS with bilateral ring mode monopolar stimulation shared between levels 2 (contacts 2, 3 and 4) (70%) and 3 (contacts 5,6 and 7) (30%), leading to further improvement of residual symptoms in the lower limbs. One month later, in the context of recurrence of intermittent axial dystonia and blepharospasm, child was closely monitored, and battery reload controlled. Since clinical aggravation continued with the patient bedridden, she was admitted to our hospital to explore eventual triggering factors, to assess DBS functioning and adjust it.

Several hypotheses were raised for the dystonia worsening; i) DBS therapy/system related; ii) triggering factors related (infection, medication alterations); iii) related to disease progression with ongoing symptom worsening. i) We first controlled DBS system impedances to rule out system dysfunction, with measures within normal range bilaterally, except for contact 3 and contact 8 (not activated) on the right electrode. These mild unilateral impedance increase (one segment out of the six active contacts) was not sufficient for explaining such a major, bilateral and progressive (over several weeks) clinical worsening. X-ray studies performed in emergency were not contributive due to motion artefacts. ii) Because of chronological inconsistency, deferiprone cessation responsibility was ruled out together with other triggering factors. iii) The main hypothesis remained disease progression. Multiple DBS and medication adjustments did not lead to significant clinical improvement. A second X-ray using MEOPA® to release relentless dystonic spasms during exploration documented bilateral full extension cable fracture in their cranial segment (Figure, part b.), despite persistent unaltered impedance measurements. Surgical replacement of the two extension cables was followed within 4 days, by a progressive improvement of the permanent and painful dystonic spasms, sweating, sleep time, and feeding allowing discharge at day 16 post-revision.

3. Discussion

Our case highlights the good initial effect of GPi DBS on dystonia in a child with PKAN, and worsening following fracture of extension cables, that surprisingly did not affect impedances. Lead fracture occurs in 1–5% of DBS patients [6], usually in the craniocervical junction, related to repetitive involuntary neck movements. System fracture results in an open circuit, leading to high electrode impedances (>10.000 Ω) and low current measures in all or some of the electrodes. One should distinguish between the electrode impedance (or lead integrity impedance) and the therapeutic impedance.

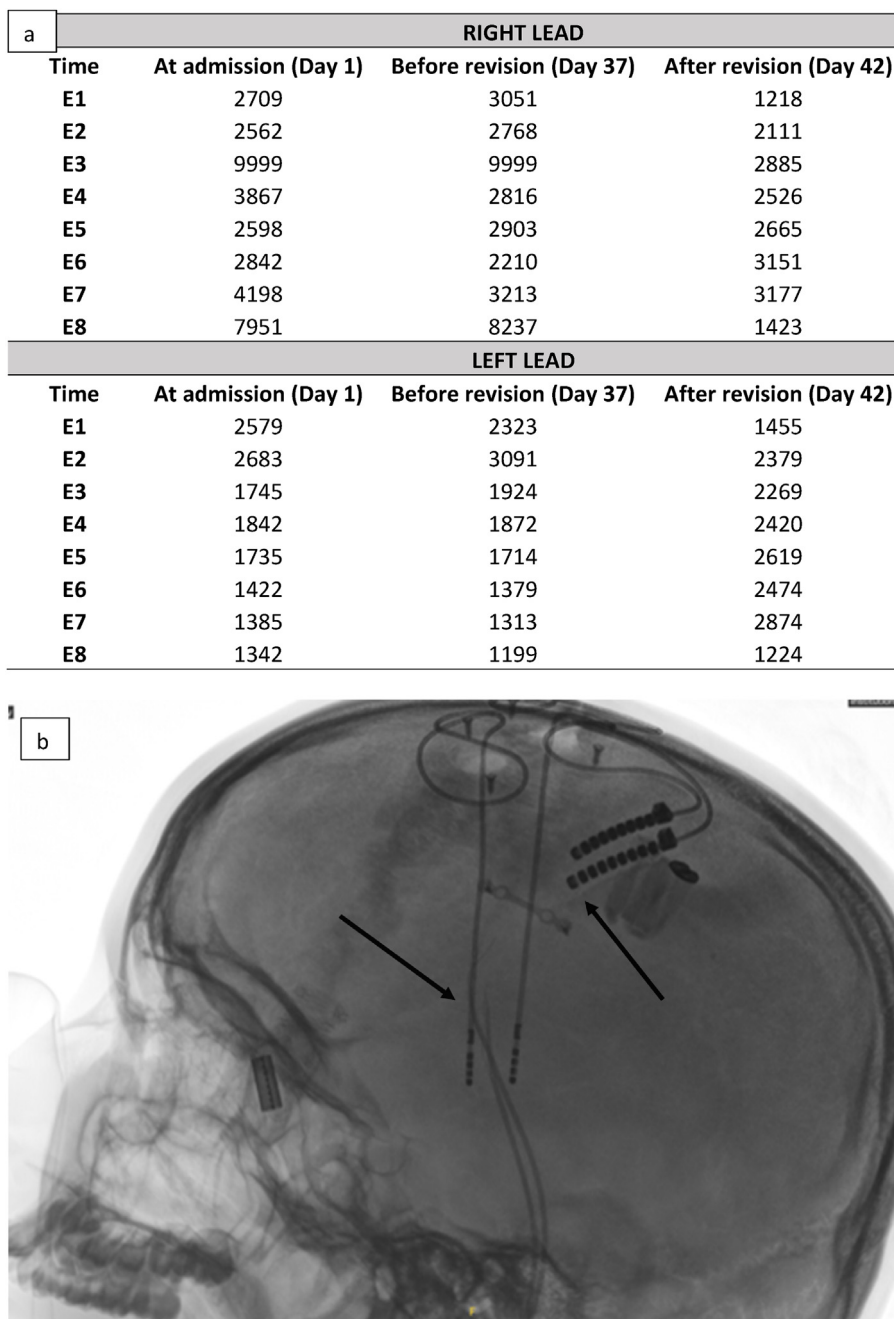


FIGURE 1. Progression of lead impedance measures and X rays documenting DBS system dysfunction
 a. Lead integrity impedances evolution at the time of the clinical worsening and following DBS system integrity restoration. Impedances measured in ohms.b. X-rays documenting bilateral extension cable fracture. Breakage of extensions underneath connection of extension (gap between the two arrows).

The electrode impedance provides information regarding the integrity of the implanted system, and refers to impedance measured automatically for each electrode configuration in both monopolar and bipolar polarity, with a low error risk <4% [7]. The therapeutic impedance refers to impedance measurements of the active contacts with the patient’s actual stimulation parameters. Impedance values vary typically between 500 and 1500 Ω, with high values measured up to 40 000 Ω for electrode impedances and 4000 Ω for therapeutical impedances. Complete fractures of leads or extension cables are usually seen on X-rays; however they may be visible only with microscopic inspection. In our patient, the apparent normality of the system integrity upon measuring impedances

together with expected progression of disease symptoms in a degenerative disorder delayed the surgical revision. Initially, neither X-rays (motion artefacts) nor impedance measurements could help documenting the DBS system fracture. It could also be hypothesized that the cable fracture was progressively completed over weeks, with consequent full dysfunction of the system due to increasing opisthotonic spasms. Only two publications reported on the absence of generalized impedance abnormalities despite complete DBS lead fracture, as documented in one of these cases through the open wound [8,9]. Elongation instead of firm fracture, still allowing interaction between the environmental tissues and DBS system, appears to be responsible for normal (or seemingly

normal) impedances in both cases. Manufacturer's information related to device architecture may provide further tools in assessing eventual DBS system dysfunction. For the Vercise system, there are two (one distal and one proximal) larger non-segmented, non-directional contacts, with lower values for normal impedances when compared to the segments of the two directional contacts in between. This could help to suspect DBS system dysfunction if the specific impedance "signature" according to the electrode size is lost, even if impedance values still fit within normal range (Figure, part a).

The most frequently used internal pulse generators (IPG) employ constant voltage stimulation. Technological developments progressed with constant current use instead of constant voltage, as in our case. Constant current IPGs offer a constant current density delivery by automatically adjusting the voltage to impedance change. Boston Scientific system does not provide therapy impedance measurement facilities.

Impedance checking is mandatory at each follow-up visit in DBS treated patients, even in the absence of symptom worsening. This ensures the maintain of an efficient therapy and may prevent further complications. Ongoing abnormal stretching of extension cables may lead to progressive increase of impedance values. Even if X-rays and impedances look normal, some authors propose surgical exploration in case of loss of the clinical effect [10], especially in severe, potentially fatal clinical conditions, such as pre-status or status dystonicus [5].

In conclusion, DBS therapy may be efficient to treat severe symptoms in pediatric movement disorders related to *PANK2* gene, as repeatedly documented in our patient: i. clinical improvement at therapy initiation, ii. clinical worsening following DBS discontinuation due to the implanted system dysfunction and, iii. clinical improvement at therapy restoration, following surgical revision. The validity of impedances measurements, even if normal, should be systematically questioned in case of clinical worsening, especially in systems applying a constant current therapy in which the automated calculation of impedance values is not provided.

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