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Case Report
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Intrathecal Administration of Nusinersen in Patients with SMA1: Too Little is Known

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Abstract

Spinal Muscular Atrophy (SMA) is a severe disease for which no curative treatment has been found. There are studies evaluating the use of nusinersen in patients affected by SMA to improve motor function and prolong their survival. We present a rare case of triventricular hydrocephalus occurred in a child affected by SMA type I, undergoing nusinersen treatment administered intrathecally. In contrast to the different studies that have evaluated the safety of nusinersen and have not reported significant adverse events, we support the hypothesis that such treatment may have severe adverse events. This seems to be in agreement with what published by the Italian Drug Agency which reported the occurrence of communicating hydrocephalus in patients with SMA treated with nusinersen. Further studies are necessary to verify the safety of Nusinersen in patients who already have such a complex and severe disease as patients with SMA type I.

Keywords: Spinal Muscular Atrophy; Nusinersen; Therapy; Hydrocephalus; Pediatrics; Neurology

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Introduction

Spinal Muscular Atrophy (SMA) is a genetic disorder caused by the mutation of the Survival Motor Neuron gene 1 (SMN1), determining the degeneration of the spinal anterior horn cells. There are four primary types of SMA (I, II, III and IV). Of these, type I is the most severe form, presenting in children who have never been able to sit independently. Up to a few years ago only supportive therapy was available, but in September 2017 the antisense oligonucleotides drug nusinersen was approved in Italy to treat patients affected by SMA. Nusinersen acts by modulating pre-messenger RNA splicing of SMN2, a second SMN gene which is not mutated in Spinal Muscular Atrophy, hence increasing the synthesis of the SMN protein [1]. So far, no serious adverse events related to nusinersen have been described [2]. Nevertheless, recently the European Medicines Agency EMA, the Italian Drug Agency AIFA and the Journal Reactions Weekly published data on five cases of hydrocephalus, not caused by meningitis or bleeding, in patients treated with nusinersen [3-5]. We describe the case of a triventricular hydrocephalus occurred in a child affected by SMA type I (SMA1) receiving nusinersen.

Case Presentation

A 7-year-old boy was admitted to our Center to perform routine follow-up according to recommended guidelines for patients affected by SMA [6]. The onset of its disease was at 15 days of life with generalized hypotonia and respiratory distress. A genetic analysis was performed showing a homozygous deletion of exons 7 and 8 in the SMN1 gene, with two copies of the SMN2 gene, confirming the clinical diagnosis of SMA1 at the age of two months. At that age, a brain MRI showed a normal ventricular system and a slightly bilaterally enlarged peri-encephalic space in the temporopolar area. Due to respiratory distress associated with CO_2 retention, non-invasive ventilation was started even before the diagnosis of SMA1 and the patient underwent a tracheotomy surgery at 17 months of life and, after a month, a tracheostomy. On that occasion, a Percutaneous Endoscopic Gastrostomy (PEG) was also placed. By the age of six years (February 2017), the patient was included in the Expanded Access Program (EAP) for nusinersen therapy

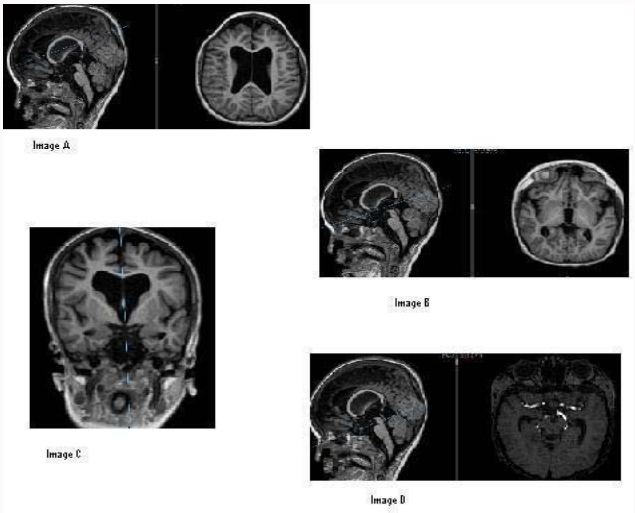

Figure 1: Bilateral papilledema with tortuosity and dilation of vessels was suddenly observed during routine fundus examination with binocular indirect ophthalmoscopy. Image A: Axial view passing through lateral ventricles; Image B: Axial view passing through mid portion of third ventricle; Image C: Coronal view of lateral and third ventricles passing to Monro Foramina; Image D: Axial view passing through temporal horns of lateral ventricles.

Figure 2: Lateral and third ventricles dilatation, without transependimal transudation and intracranial hypertension signs.

in SMA1 at the Nemo Center for Neuromuscular Disorders in Messina, Italy. Nusinersen is antisense oligonucleotides that are administered by lumbar puncture bolus injection, available in Italy for patients with SMA1 diagnosis only within an EAP. The intrathecal administration of nusinersen was performed on treatment days 0, 15, 30, 60 and subsequently every four months at the dosage of 12 mg. Last administration of nusinersen was given in August 2018. No change in the Chop Intend scale was observed during the treatment period and after the last administration (August 2018) he was still given a score of 0 [7]. No adverse event was observed during the treatment, and no difficulties in the intrathecal administration were reported. When the child was admitted to our Center, one month after the last nusinersen administration, he appeared in stable and satisfactory general conditions. The neurological examination revealed severe muscular hypotonia and hypotrophy, no head control, no active movement of upper or lower limbs and bilateral palpebral ptosis, which was first seen at 2 years of age on the left, involving the right side after one year. The boy was able to use an optical pointer to communicate. He did not show any apparent signs or symptoms caused by intracranial hypertension. Because of the bilateral ptosis, the patient was evaluated by an ophthalmologist. A

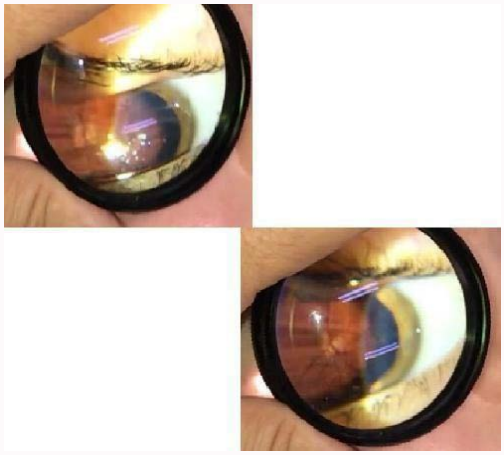

Figure 3: Fundus examination with indirect ophthalmoscopy after therapy of intracranial hypertension: resolution of papilledema after treatment.

fundoscopic examination showed signs of bilateral optic disk edema: the disks were of normal color, slightly elevated, with blurred margins and vascular tortuosity at the emergence of the optic nerve (Figure 1). A brain MRI with gadolinium and MR angiography revealed a localized enlargement of the peri-encephalic space in the retro-cerebellar, temporopolar and base area, also involving the cerebral convexity. The presence of an enlargement of the ventricular system in the supratentorial compartment was compatible with triventricular hydrocephalus; signs of transependimal reabsorption were not detectable. A neurosurgical approach was not necessary (Figure 2). In order to evaluate the presence of intracranial hypertension, a lumbar puncture with manometry was executed. It confirmed the presence of intracranial hypertension, with a measured pressure of 480 mm H2o in the presence of normal blood pressure (BP 108/65). The boy started medical therapy with acetazolamide at a dose of 16 mg/kg TID followed by an improvement of the optic disk edema after 10 days: the disks were no longer elevated, retinal blood vessels normalized while the margins were still blurred. Because of intolerance (vomiting and electrolytes imbalance) our patient's therapy was switched to topiramate (0.5 mg/kg BID). The fundoscopic exam performed after 2 months of therapy showed a normal optic disk (Figure 3). Our patient will continue topiramate therapy for 6 additional weeks and will then repeat the MRI.

Discussion

SMA is a neuromuscular genetic disorder affecting the lower brainstem nuclei and the spinal cord resulting in proximal muscle weakness and atrophy. SMA1 is the most severe form of the disease, with an estimated incidence of 1 in 6000 to 10000 live births [8]. The onset of symptoms occurs in the first six months of life and the life expectancy is about 2 years in the absence of supportive therapy [9]. Nusinersen is an antisense nucleotide molecule that acts in the process of pre-RNA splicing of SMN2, increasing the synthesis of the SMN protein [1]. In a phase two, open label study, the intrathecal administration of nusinersen in patients with SMA1 improved motor function and survival. Specifically, 41% of the patients treated with nusinersen presented a milestone-motor response, defined according to the Hammersmith Infant Neurological Examination, versus 0% of patients of the control group [10,11]. Nusinersen safety was evaluated in several studies and no significant adverse event related to the drug and the intrathecal administration was detected by the authors

[12,13]. In opposition to these data, the Italian Drug Agency has reported the occurrence of communicating hydrocephalus in patients with SMA treated with nusinersen but detailed information about these cases are not available [5]. Our patient presented a triventricular hydrocephalus with intracranial hypertension during nusinersen therapy. The child did not present symptoms of intracranial hypertension and the findings of papilledema, hydrocephalus and intracranial hypertension were unexpected. The investigations performed did not reveal any infectious, malformative or vascular cause that could have been responsible for the onset of this condition. Therefore, we suppose that the hydrocephalus could have been caused by the intrathecal administration of nusinersen and we believe that further studies are necessary to assess the risk-benefit ratio of intrathecal therapy with nusinersen. As nusinersen is a new drug, so far used in a relatively small number of SMA patients, we consider it important to present our case, especially because of the severity of the adverse event observed. It might be possible that nusinersen causes an imbalance between cerebrospinal fluid's production and absorption. Also, the possible role of repeated lumbar punctures in the development of hydrocephalus and intracranial hypertension should be discussed.

Conclusion

Our case supports the hypothesis that such treatment may cause severe adverse events and therefore we believe that further studies are necessary to verify the safety of this therapy in patients who already have such a complex and severe disease.

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