Research Article

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A Case of Sagittal Sinus Thrombosis after the First Dose of Intrathecal Nusinersen Treatment

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Abstract

Spinal Muscular Atrophy is a progressive autosomal recessive motor neuron disease caused by the loss of the SMN1 gene. Nusinersen is an antisense oligonucleotide that produces an effect by increasing SMN protein production. Despite the studies that demonstrated improved motor function and milestones in infants and children after intrathecal nusinersen treatment, side effects were also reported.

Aim: *In this paper, we report our experience with 16 years old boy with spinal muscular atrophy that experienced sagittal sinus thrombosis five days after the first dose of intrathecal nusinersen treatment.*

Material and method: *The patient experienced severe headache, nausea, vomiting, epistaxis, and gradually increased neck stiffness. Magnetic Resonance Image showed thrombosis in the superior sagittal sinus and a pachymeningeal enhancement, venography showed filling defect. Enoxaparin was started. The nusinersen treatment was stopped.*

Conclusion: *The adverse effects of nusinersen are still a puzzle. Increased intracranial pressure clinical manifestations such as prolonged headache, nausea, vomiting after intrathecal nusinersen treatment should be taken seriously and the possibility of a sinus thrombosis should be kept in mind.*

Keywords: Spinal Muscular Atrophy, Nusinersen, Stroke.

Introduction

Spinal Muscular Atrophy (SMA) is a disorder characterized by degeneration of motor neurons leading to progressive muscle weakness (Biogen, 2016; Hoy, 2017). In December 2016, nusinersen is approved for all types of SMA by the food and drug administration (FDA) after studies demonstrated improved motor function and milestones in infants and children (Hoy, 2017; Michelson et al., 2018). The side effects of nusinersen are still not fully known. The most common side effects were consistent with conditions associated with childhood in general and SMA specifically (pyrexia, cough, pneumonia, upper respiratory tract infection).

In this paper, we report our experience with 16 years old boy with SMA that experienced sagittal sinus thrombosis after the first dose of intrathecal nusinersen treatment.

Case Presentation

A sixteen years old boy who had difficulty in walking after 6 years old, fasciculation in tongue muscles, absence of deep tendon reflexes was diagnosed genetically and clinically as SMA type 3. He was the fourth child of consanguineous parents. All the other siblings were healthy. The pregnancy was uneventful, he experienced low muscle tone at 6 years old and difficulty in running and climbing stairs. There was a homozygous deletion in 5q- SMN1 and the copy number of SMN2 was 3.

A Complete Blood Count (CBC) and biochemical analysis were normal. The patient did not have a known history of thrombosis, bleeding and there were no dehydration signs or bacterial, viral infection symptoms. There was no history of any cerebrovascular accidents in the family. After 5 days of receiving the first dose of intrathecal nusinersen, the patient experienced severe headache, nausea, vomiting, epistaxis, and gradually increased neck stiffness. The measured temperature was 36,7°. On physical examination, he was conscious and expressed severe neck stiffness. No kernig and brudzinski was seen. Cranial nerves examination and cerebellar tests were

normal. Babinski reflex was a planter. There was papilledema of the optic disc on ophthalmic examination. Acute phase reactants were normal. On lumbar punction, the cerebrospinal fluid pressure was 40 mm H_2O. Protein and glucose were 39,2 mg/dl and 67 mg/dl, respectively, and normal cell counts were found. Magnetic Resonance Image (MRI) showed thrombosis in the superior sagittal sinus and pachymeningeal enhancement, venography showed filling defect (Figure -1).

CBC, homocysteine, B12, folate, serological panel, C3, C4, ana, anti-DNA, APTT, PT, and INR were normal. In the thrombotic factor examination, no abnormality was found except heterozygous polymorphism in the MTHFR gene (C677T, A1298C). Enoxaparin was started and nusinersen treatment was stopped and never planned again.

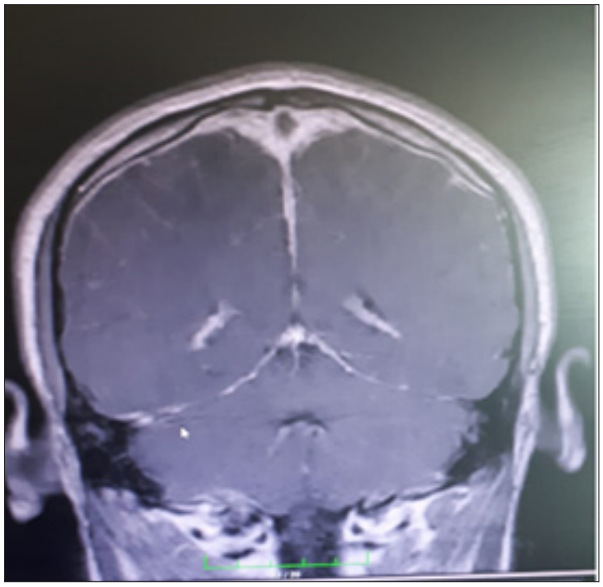

Figure1: Coronal sequence, A sixteen years old patient with SMA, cerebral neuroimaging shows thrombosis in the superior sagittal sinüs and pachymeningeal enhancement

Discussion

Despite the beneficial aspects of nusinersen on motor function and milestones in infants and children, its benefits in adults are still unclear. Besides intrathecal nusinersen side effects are reported (Darras et al., 2019; Aslan et al., 2019).

The effects and adverse effects of this drug have not been revealed completely. Some reported side effects were related to intrathecal administration rather than the drug itself and some effects are related to the drug itself which can be mild like backache, fever, and vomiting. Serious side effects like pneumonia, skin rash, complete or partial atelectasis, damage to the kidneys, thrombocytosis, epistaxis, and bleeding due to clotting disorder, decreased blood platelets, meningitis not due to infection, hyponatremia, hypersensitivity reaction, acquired communicating hydrocephalus were also reported, Our patient experienced signs and symptoms of increased intracranial pressure as a result of sagittal sinus thrombosis five days after the first dose of intrathecal nusinersen treatment. Increased intracranial pressure clinical manifestations such as prolonged headache, nausea, and vomiting after intrathecal nusinersen treatment should be taken seriously and the possibility of a sinus thrombosis should be kept in mind (Aslan et al., 2019; Goodkey et al., 2018; Ko et al., 2019).

Cerebral Sinus Venous Thrombosis (CSVT) is a disease that can be seen in all age groups with different clinical findings and mostly with a good prognosis. The most important known etiologies are pregnancy, oral contraceptive drugs, systemic inflammatory disease, malignancy, coagulation disorders, and hematological disease. MTHFR gene polymorphisms (C677T, A1298C) presenting a risk factor alone or through homocysteine levels is controversial. The incidence of these polymorphisms in healthy individuals has also been reported, in our case, whether CSVT occurrence is due to the nusinersen or due to MTHFR (C677T, A1298C) mutation is still unclear. This study cannot make causal inferences on the relation between nusinersen and MTHFR (C677T, A1298C) mutation due to the absence of previous stroke history and occurrence of thrombosis after the first dose of intrathecal nusinersen made us think of the strong relationship between this drug and sagittal sinus thrombosis as a causative factor (Ayas et al., 2018; Chiriboga, 2017).

In a study, of 15 patients who had CSVT 2(13.3%) were determined to carry heterozygous homozygous MTHFR C677T mutation. Seven out of 15 (46.7%) patients investigated for MTHFR A1298C mutation were determined to have heterozygous and 1 of them to have a homozygous mutation. These mutations are clinically relevant if they cause hyper homocysteinemia. Our patient's homocysteine level was 3.1 mg/dl and he did not have any problems till the first intrathecal dose of nusinersen treatment which to the best of our knowledge, is the first SMA patient to develop a stroke after nusinersen treatment (Ayas et al., 2018; Chiriboga, 2017; Walter et al., 2019).

Conclusion

The adverse effects of nusinersen are still unknown. Increased intracranial pressure clinical manifestations such as prolonged headache, nausea, and vomiting after intrathecal nusinersen treatment should be taken seriously and the possibility of a sinus thrombosis should be kept in mind.

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Informed consent statement: The parents or the child's legal guardians provided informed written consent before study enrollment.

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