



Case Report

Novel Complication of Nusinersen Treatment: Hyponatremia

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Abstract

There are variations in therapeutic regimens of different liver diseases. The accurate diagnosis ensNusinersen treatment is a novel therapy for spinal muscular atrophy (SMA) type 1; consequently, the adverse reactions of the therapy, have not been well known, yet. The present study is a case report that declares a hyponatremia development after the nusinersen therapy. Since the therapy is quite new one and has limited practice, we hope that this rare complication will contribute to the scientific literature.

Introduction

Nusinersen (SPINRAZA-Biogen; Cambridge, MA, USA) has received the first global approval on 23 December 2016 for the treatment of SMA in paediatric and adult patients in the United States Food and Drug Administration (FDA) [1]. Most common adverse reactions are: lower respiratory tract infection, upper tract respiratory congestion, skin rash, back pain, proteinuria and postlumbar puncture syndrome. Severe hyponatremia was reported before in an infant SMA patient, treated with nusinersen. The researchers reported that, salt was added to his diet during 14 months because of severe and resistant hiponatremia [2]. The present report is another case of hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), induced a single dose of nusinersen treatment.

Case Report

A 5-month-old boy diagnosed with SMA type 1 was admitted to our pediatric intensive care unit for the second dose nusinersen therapy. He received the first nusinersen therapy two weeks ago. His physical examination and vital signs revealed no abnormalities. Laboratory findings on the day of admission, total blood count, renal and liver function test, random blood sugar, routine urine examination, cerebrospinal fluid (CSF) examination, venous blood gas analysis and serum electrolytes except sodium were within the normal limits. Serum sodium concentration in venous blood gas analysis was 110 mmol/L; and this result needed to be confirmed by a subsequent laboratory blood sample analyse. However, serum sodium level was found to be 109 mmol/L, again. There was no history of hyponatremia, suggestive water intake, vomiting or diarrhea, before nusinersen treatment. He was fed with breast milk by a nasogastric tube and gained only 500 gr during the last month. There were no signs of dehydration and generalize/localize edema. His laboratory findings were as follows: lipid profile and blood sugar are within normal range; blood urea: 3,38 mg/dL; creatinin: 0,04 mg/dL; uric acide: 1,5 mg/dL; sodium: 110 mmol/L; potassium: 4,2 mmol/L; urine density: 1.002. His thyroid and adrenal functions were normal. His renal ultrasonography was reported as normal. Further investigations revealed low serum osmolarity (260 mOs/L), elevated urine



osmolarity (110 mOsm/L) and random urine sodium levels (30 mEq/L) based on which the diagnosis of SIADH was made. Antidiuretic hormone (ADH) level analysis could not be done at the hospital laboratory. His nutrition was added with table salt and he was discharged on day 5th. Follow-up blood tests a week later showed that the results had returned to normal ranges with serum sodium level 132 mmol/L, with added table salt. Firstly, water intake was restricted, then hypertonic saline given to increase the sodium level by 10mEq/L within 24 hours. The patient continues to get nusinersen treatment, and can only keep normal sodium levels with added table salt. Another complication due to nusinersen did not develop.

Discussion

Spinal muscular atrophy is a genetic disease characterized by muscle weakness resulting from the degeneration of alpha motor neurons in the spinal cord and the brainstem [3]. Usually, SMA is caused by a homozygous deletion of the SMN1 gene, resulting in SMN protein deficiency. The SMN locus contains a paralog SMN2 due to an inverted duplication on human chromosome 5 [4].

Nusinersen is an antisense oligonucleotide that leads to splicing correction of the SMN2 gene [5]. The drug is administered intrathecally at 12 mg and 4 dose loading is recommended at the beginning. Nusinersen gets cleared from CSF into the systemic circulation and is quantifiable for 15-168 days after dosing. Autopsy data exposed the presence of nusinersen in liver, skeletal muscles, and kidney situation show that nusinersen gets cleared from CSF into the systemic circulation. Nusinersen is metabolized via exonuclease-mediated hydrolysis. The mean half-life of nusinersen 63-87 days in the plasma. The primary route of elimination is thought to be via urinary excretion [6].

Adverse effects of novel therapy nusinersen were investigated by large clinical trials such as ENDEAR, CS3A, CHERISH and NURTURE [6]. CS3A clinic trials reported three cases, which developed hyponatremia. One of them is, a four-month-old girl, who diagnosed SMA type 2, had developed hyponatremia on 89th days after treatment and on 231st day, Na level was determined as 96 meq/l. This patient was supported with table salt, during 14 months [7]. The other case was a 2-month-old boy, a hyponatremia was determined on the 184th day of the treatment. However, the hyponatremia was not thought to be related with the drug and was attributed to bronchiolitis, levetiracetam and high fever [7]. The third patient was 7-month-old baby and on 190th day of the treatment, hyponatremia was diagnosed. Since he had weight losses and diagnosed with pneumonia; hyponatremia was not recorded to be associated with nusinersen therapy [7].

Because of these three reports, Center for Drug Evaluation and Research, suggests to control serum sodium, both before and after nusinersen treatment. Nusinersen-induced hyponatremia, was admitted in only one case and the mechanism was not explained [7]. In present case, our patient developed a hyponatremia following the first nusinersen therapy and that occurred at slowly onset. The patient was examined, with regard to inappropriate secretion of antidiuretic hormone etiological factors, as presented in table 1, such as pain, nausea, stress, and numerous pharmacological agents and diseases [8]. He was ventilated by using home ventilator, for 3 months but, hyponatremia had not developed until the nusinersen therapy. Consequently, no reason was found to explain the etiology of hyponatremia, except for nusinersen administration.

In conclusion, it is suggested that when developing medicine like nusinersen and other oligonuclear ones, this rarely seen but significant complication that stated in present case should be taken into consideration. In addition, the case report is expected to contribute the related literature, for future implementations.



Table 1: Causes Of Syndrome Of Inappropriate Secretion Of Antidiuretic Hormone In Children

Acute Conditions	Pulmonary Disease	Neurological Diseases	Medications	Malignant Disease	Hereditary Causes
General anesthesia	Positive pressure Ventilation	Meningitis, encephalitis	Carbamazepine	Lymphoma	Gain of function mutation V2R
Stress	Bronchiolitis	Tumors	Vincristine	Ewing sarcoma	
Nausea	Pneumonia	Trauma	Cyclophosphamide	Carcinoma (lung, bladder, etc)	
Pain	Asthma	Hydrocephalus	Tricyclic antidepressants		
Stress	Cystic fibrosis	Brain abscess	Narcotics		
		Rocky mountain spotted fever	NSAIDs		
		Cavernous sinus thrombosis	MDMA (ecstasy)		
		Guillain-Barré syndrome	SSRI		
		Cerebrovascular accident	Desmopressin		
		Subdural hematoma	Ciprofloxacin		
			Amiodarone		

For a complete list, see references 1 and 2. MDMA¼3,4-methylenedioxymethamphetamine, NSAIDs¼nonsteroidal anti-inflammatory drugs, SSRI¼selective serotonin reuptake inhibitor; V2R¼vasopressin 2 receptor.

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