Novel complication of nusinersen treatment: Hyponatremia

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Abstract

Nusinersen is a novel therapy for spinal muscular atrophy (SMA) type 1. Thus, the adverse reactions of the therapy have not been well established. We present here a 5-months old boy with SMA type 1, who developed hyponatremia after a single dose of nusinersen which has been rarely reported previously.

INTRODUCTION

Nusinersen (SPINRAZA-Biogen; Cambridge, MA, USA) has received the first global approval on 23rd December 2016 for the treatment of SMA in paediatric and adult patients in the United States Food and Drug Administration (FDA). 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 in an infant SMA patient, treated with nusinersen. The investigators reported that salt was added to his diet for 14 months because of severe and resistant hiponatremia. We report here another case of hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), after 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 earlier. His physical examination and vital signs revealed no abnormalities. The laboratory findings on the day of admission before the nusinersen treatment showed that the 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 other than sodium were within normal limits. Serum sodium concentration in venous blood was 110 mmol/L; this was confirmed by a subsequent laboratory blood sample analyse of 109 mmol/L. There was no history of excessive water intake, vomiting or diarrhea, or similar history in the past to explain the hyponatremia. He was fed with milk by a nasogastric tube and gained only 500 gram during the last month. On examination, there were no signs of dehydration, general or local edema. His other laboratory findings were: lipid profile and blood sugar were within normal range; blood urea: 3.38 mg/dL; creatinin: 0.04 mg/dL; uric acide: 2.4 mg/dL; sodium: 110 mmol/L; potassium: 4.2 mmol/L; urine specific gravity: 1.002. His thyroid and adrenal functions were normal. Further investigations revealed low serum osmolarity (260 mOs/L), elevated urine osmolarity (110 mOs/L) and random urine sodium levels (30 mEq/L), based on which the diagnosis of SIADH was made. Antidiuretic hormone (ADH) level could not be done at the hospital laboratory. Table salt was added to his nutrition, 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 of 132 mmol/L on added table salt. The patient continued to get nusinersen treatment, and could only maintain a normal sodium levels with added table salt. There was no other complication due to nusinersen treatment.

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. 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.\textsuperscript{4}

Nusinersen is an antisense oligonucleotide that leads to splicing correction of the SMN2 gene.\textsuperscript{5} Nusinersen gets cleared from CSF into the systemic circulation and is quantifiable for 15-168 days after dosing. Pharmacokinetic studies show the presence of nusinersen in liver, skeletal muscles, and kidney; and nusinersen gets cleared from CSF into the systemic circulation. The primary route of elimination is thought to be via urinary excretion.\textsuperscript{6}

Previous clinic trials (CS3A) have reported three cases of nusinersen treatment induced hyponatremia. However, only one case was admitted and the mechanism of the hyponatremia was not explained.\textsuperscript{7} Our patient developed a hyponatremia following the first dose of nusinersen therapy. The patient was investigated for causes of inappropriate secretion of antidiuretic hormone such as pain, nausea, stress, and numerous pharmacological agents and diseases according to Jones \textit{et al.}\textsuperscript{8} There was no reason to explain the etiology of hyponatremia, except for nusinersen administration.

In brief, we presented a case of hyponatremia from SIADH following the first dose of nusinersen, confirming the risk of developing hyponatremia with its use.

**DISCLOSURE**

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**REFERENCES**

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