Recurrent episodes of hypoglycemia in an infant with type 1 spinal muscular atrophy after gene therapy: Beta oxidation defect exaggerated by hepatic dysfunction.

Nada Alaaraj1, Noor Hamed1, Ashraf Soliman1, Tawfeg Ben Omran2

1.Department of pediatric, Hamad general hospital, Doha-Qatar.

2. Department of genetics, Sidra Medicine, Doha-Qatar

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease. In 2016, nusinersen (Spinraza) was approved by the FDA. The first AAV9-based gene therapy (Zolgensma), was approved by the FDA (2019) for the treatment of infants with SMA.
We report an SMA case with recurrent hypoglycemic events after gene therapy.

Case Report

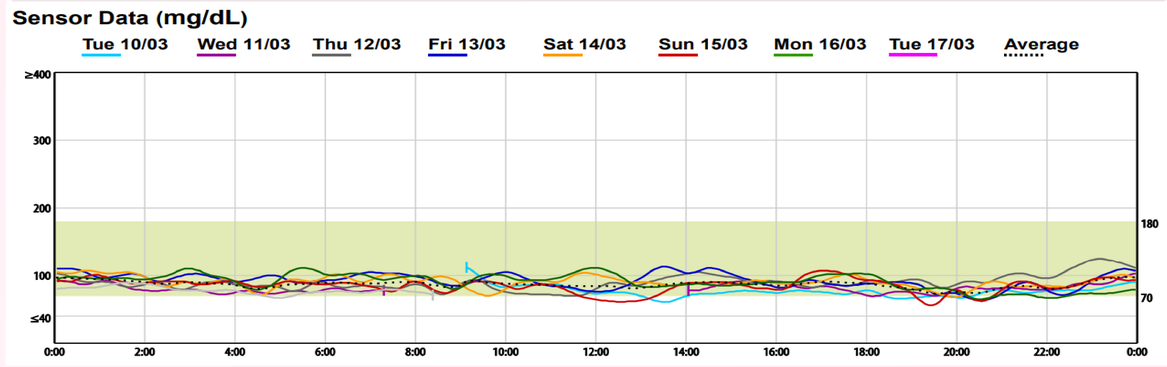
A 22 months old boy, with SMA type 1 was born at term by CS for fetal bradycardia. Initially, he was fed orally well with progressive swallowing difficulties. He was floppy with a weak Moro reflex. He had a positive family history of confirmed SMA. Both parents were carriers for the SMA gene and had another 3 healthy children.

- He was started on Spinraza by day 12 of life after genetic diagnosis and received 7 doses. At 6 months of age, he received intravenous gene therapy (GT) and 1mg/kg/day prednisolone as per protocol.

One week after GT, his liver enzymes (ALT and AST) were elevated (65 and 127U/L, respectively). Three weeks later, while on prednisolone therapy, he developed an episode of hypoglycemia (1.9 mmol/L) 1.5 hours after feeding. He was receiving high caloric formula for low BMI.
During another attack of hypoglycemia (BG= 2.8 mmol/L), the levels of insulin = 2.4 mic unit/ml, B-hydroxybutyrate 0.06mmol/L(low), cortisol 33.8nmol/L (low), and GH 1.77ug/L(low). While on prednisolone therapy and continuous GJ feeding, he had no hypoglycemia. After discontinuation of prednisone, a trial of interrupted feeding resulted in an episode of hypoglycemia (2.2mmol/L) after 0.5hour. Critical sample showed BG =2.4mmo/L, B-hydroxybutyrate = 0.54mmol/L, insulin =0.9 mic uint/ml, cortisol =132 nmol/L, GH = 8.69ug/L, and no acidosis.
Continuous glucose monitoring (CGM) showed a generalized tendency to low glucose readings with the lowest = 3 mmol/L.
These data of non-kenotic hypoglycemic episodes supported the possibility of associated fatty acid oxidation defect. His amino acid pattern and acylcarnitine screening were normal.

Labs and Figures

Critical sample	1st sample	2nd sample
Blood glucose (mmol/L)	2.8	2.4
Insulin (N:0.4-32.6 mU/ml)	2.4	0.9
B-hydroxybutyrate (mmol/L)	0.06	0.54
Cortisol (N:58-567nmol/L)	33.8	132
GH (N: >10ug/L)	1.77	8.69



Conclusion

Hypoglycemia is a major clinical sign in all fatty acid oxidation defects due to a reduced hepatic glucose output and an enhanced peripheral glucose uptake. Zolgensma, most common side effects are elevated liver enzymes and vomiting. It appears that these side effects of Zolgensma could amplify the hypoglycemic effect of the associated FAOD in these children.

Contacts

Prof. Ashraf Soliman
atsoliman56@gmail.com
Nada Alaaraj
nadaalaaraj@gmail.com