

A case of Donohue Syndrome : New Genetic Mutation and added phenotypic characteristics.



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Abstract

Leprechaunism (**Donohue syndrome**)(DS) is an extremely rare AR disease that presents with special phenotypic features including severe type of insulin resistance with high mortality in infancy. We report a 3 month-old girl with DS with new features included exocrine pancreatic insufficiency, central hypothyroidism and severe lethal obstructive cardiomyopathy. Continues glucose monitoring (CGMS) before and after treatment with insulin and metformin was recorded.

Case Study

R 3 ½ months old Syrian girl, born at 35 weeks of gestation with Asymmetrical IUGR. She developed hyperglycemia from day1 of life >150 mg/dl (350 +/- 60 mg/dl) and her serum insulin and c-peptide were very high (**772uU/ml and 29.9 ng / ml respectively**). Insulin infusion was started with requirement between 0.4 -0.5 unit/kg/day to keep her BG < 200 mg/dl. After the first month, her insulin requirement decreased spontaneously and the insulin was stopped for 7- 10 days three times (average BG = 130 +/- 55 mg/dl despite the presence of severe hyperinsulinemia (1900 and 2875 uU/ml) . By the second month, facial dysmorphism became obvious in the form of prominent eyes and maxilla, upturned nose, large and low set ears, thick lips, gum hyperplasia, long narrow face, thick eye brows hypertrichosis of the forehead and the back, long feet and button-like nipples.

CGMS recorded average BG= 350 +/- 100 mg/dl while off insulin with fluctuating levels (hypo- and hyperglycemia) and average BG = 300 +/- 50 mg/dl) while on insulin infusion. She was started on Metformin (50 mg PO daily) as trial, and her CGMS showed a reasonably good response to metformin with average BG of 150 mg/dl compared to BG on insulin. Continuous Nasogastric feeding (NGT) aiming to prevent her pre meal hypoglycemia.

Known features of the syndrome that the patient had:

- 1-unexplained abdominal distension which worsens gradually with no evidence of organomegaly
- 2- Direct hyperbilirubinemia of (57Umol/L) and raised liver enzymes (ALT 90U/L, AST 89U/L, ALP 167U/L and GGT 114U/L) necessitated treatment with Ursodeoxycholic acid
- 3- Bartter-like picture with hypokalemia with high aldosterone level (> 4993pmol/L needed oral potassium chloride treatment 1meq per kg q8hrs
- 4- High urinary calcium to creatinine ratio of 4 (normal < 0.3), with evidence of nephrocalcinosis by KUB ultrasound
- 5- central hypothyroidism TSH 0.02 mLU/L, free T4 = 9.7pmol/L, she was started on l-thyroxine 12.5mcg/day
- 6- Progressive hypertrophic obstructive cardiomyopathy (HOCM) causing her death at the age of 3.5 months
- 7- multiple episodes of clinical sepsis

Figures

Figure 1: CGMS while patient was off any treatment

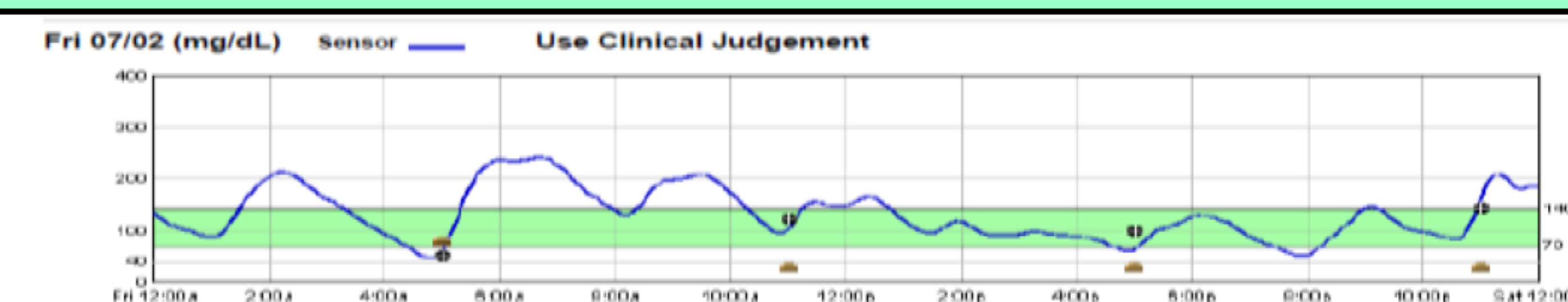


Figure 2:CGM while patient was on insulin infusion with d poor response to insulin

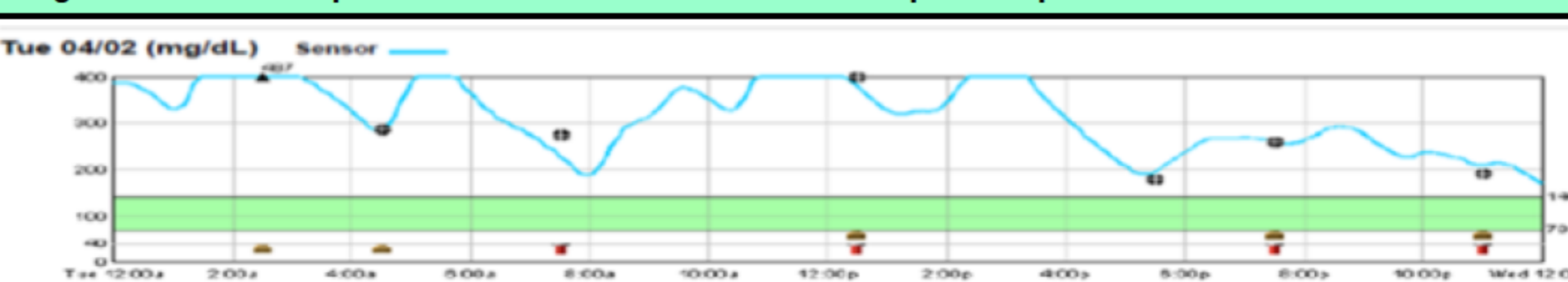


Figure 3:CGMS while on metformin showing better response compared to insulin

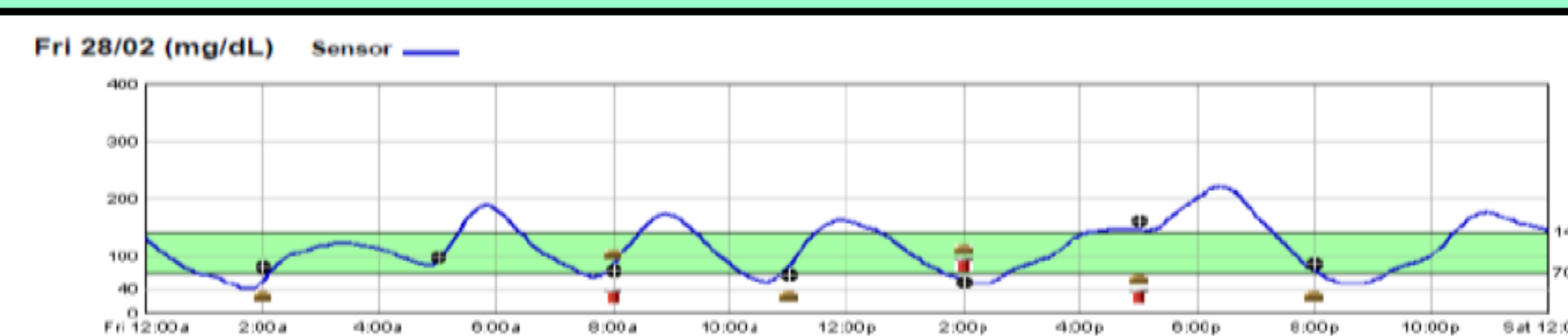
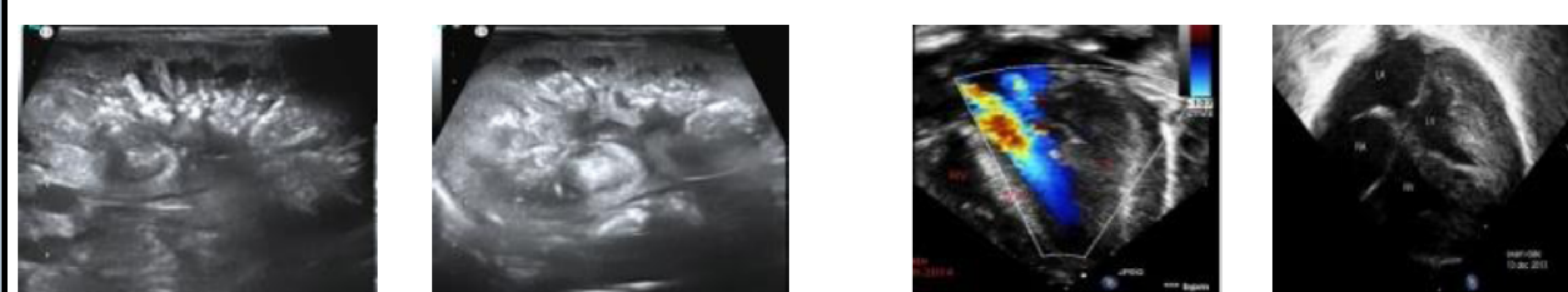
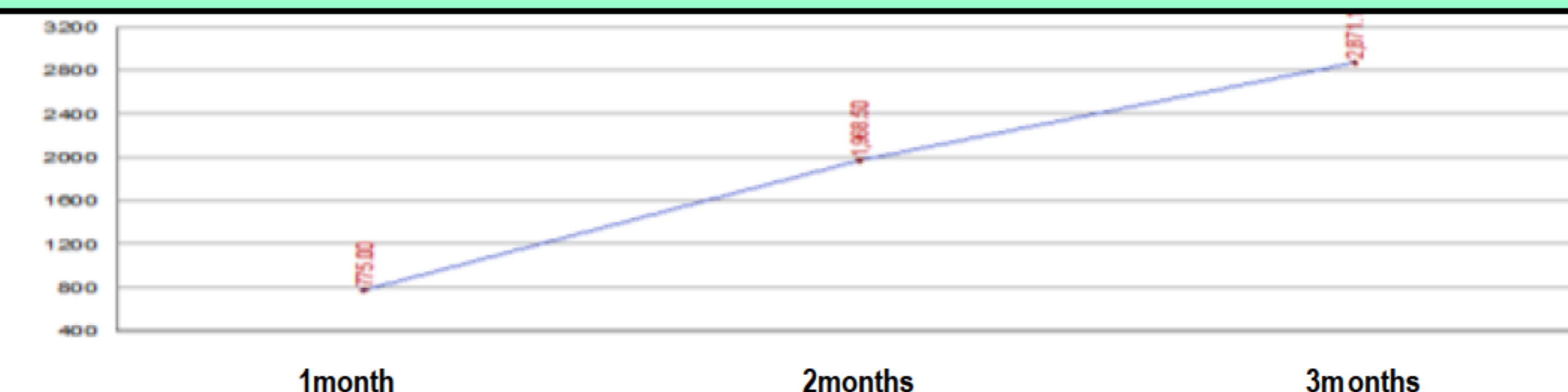


figure 4:Serum Insulin level in the first, second and third month (uU/ml)



Bilateral nephrocalcinosis

obstructive cardiomyopathy

Discussion

New features:

- 1- Monitor spontaneous glycaemia as well as response to insulin and metformin therapy using continuous glucose monitoring system (CGMS).
- 2- Metformin was successful therapy that maintained BG in the normal range most of the times
- 3- Exocrine pancreatic insufficiency, (not described before in this syndrome) was associated with improvement of weight gain with the enzyme replacement
- 4- New autosomal recessive of **INSR homozygous mutation** (c.3583A>T p.Lys1195*) with carrier parents

Conclusion

Our patient with Donohue syndrome patients has new mutation of INSR with severe but fluctuating degrees of insulin resistance, and possibly defective bio-activity of endogenous insulin, and exocrine pancreatic insufficiency. Metformin was effective in the treatment of glycemic abnormalities and pancreatic enzyme replacement improved weight gain.

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