A case of neonatal diabetes and pancreatic hypoplasia (Wolcott-Rallison syndrome)

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No conflict of interest

Abstract serial number: 240 **Poster Number: P2-P109** **Topic: Diabetes and insulin**

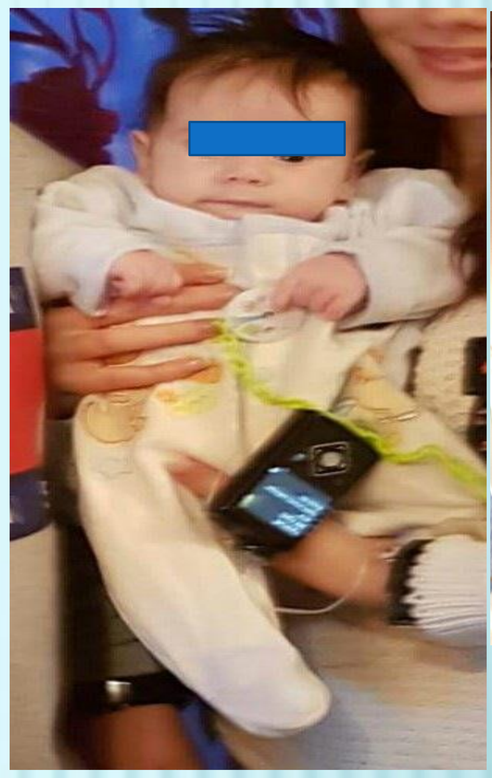
Introduction and objectives

Neonatal diabetes mellitus (NDM) is a rare form of insulin-dependent monogenic diabetes mellitus (1/400,000 live births) diagnosed in the first six months of life. It can be either transient (TNDM) or permanent (PNDM). A cause of PNDM is Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disorder characterized by the association of permanent neonatal or early-infancy insulin-dependent diabetes, multiple epiphyseal dysplasia, growth retardation, and other variable multisystem clinical manifestations. Typically, diabetes occurs before six months of age, and skeletal dysplasia is diagnosed within the first year or two of life. Hepatic dysfunction has been reported in 60% of patients. WRS is caused by recessive loss of function mutations in the *EIF2AK3* gene.

We describe a male infant, 2.5 months old with WRS, presented with PNDM and pancreatic hypoplasia.

Methods

The infant was admitted via the Paediatric Emergency Department with a two-week history of reduced feeding, irritability, failure to thrive and loose stools 6-10 times / day. He was the first child of healthy, unrelated parents, born at $40^{+3}/40$ by emergency caesarean section, IUGR, birth weight 2300gr. Clinically, he was alert, pale, with mild dehydration, vital signs normal. Biochemistry showed hyperglycaemia without ketoacidosis, blood glucose 919 mg/dl (51mmol/l), Na^+ 121mmol/L(NR 135-145 mmol/L), K^+ 5.6 mmol/l NR 3.5-5.1mmol/L), pH 7.418, $HCO3^-$ 25.3 mmol/l, BE 1.3 mmol/l), HbA_1c 13.6% (125.1mmol/mol) (NR 4-6, 20.2-42.1), C-peptide 0.449 ng/ml(NR 1.1-4.4), serum amylase 15 U/L (NR 28-100) and serum lipase 4 U/l (NR 13-60). He was treated with intravenous fluids and insulin, then with subcutaneous insulin. Diarrhoea improved gradually, and he started gaining weight and had normal stool on day 8. Subsequently, he started on CSII with synchronous continuous glucose monitoring (CGM). His development is normal for age, growth <3rd percentile, latest HbA1c is 8.1% (65mmol/mol) (Fig 1 &2).



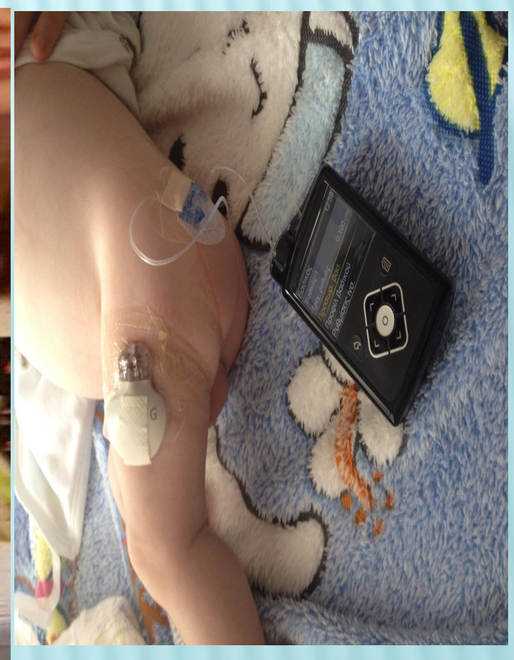


Fig.1 & 2. patient on CSII and CGM

Results and Conclusions

Antibodies to glutamic acid decarboxylase (anti-GAD) 0.1 (<10U/ml) and insulin (IA2) 8.7 (<10U/ml) were negative, pancreatic islet cell antibodies (ICA) marginally positive 1.6 U/ml (>1.05 U/ml positive). Faecal elastase was detected at very low levels (<15 grams/gr of faeces, NR >200) on two occasions. Series of abdominal ultrasounds showed a hypoplastic pancreas for age, confirmed by abdominal MRI. Genetic testing revealed that the patient is compound heterozygous for an EIF2AK3 partial gene deletion and a novel missense variant, p.(Cys215Arg), result is consistent with a genetic diagnosis of WRS syndrome. Both parents are carriers of WRS, mother is heterozygous for the EIF2AK3 partial gene deletion variant, c.(2820+61_2821- 116)_(2988+76_2989-100)del and father is heterozygous for the EIF2AK3 missense variant, p.(Cys215Arg). Both variants are predicted to be likely pathogenic. The *EIF2AK3* gene encodes a protein called pancreatic PKR-like endoplasmic reticulum kinase (PERK), which plays a key role in detecting and initiating the cellular response to endoplasmic reticulum stress. Failure of appropriate PERK response results in accumulation of misfolded proteins, which leads to cell damage and apoptosis (fig 3).

Genetic counselling and antenatal diagnosis is recommended for parents of a WRS patient with confirmed *EIF2AK3* mutation. Close therapeutic monitoring of diabetes and treatment with an insulin pump are recommended because of the risk of acute episodes of hypoglycaemia and ketoacidosis. Interventions under general anaesthesia increase the risk of acute aggravation, because of the toxicity of anaesthetics, and should be avoided. Prognosis is poor and most patients die at a young age. Intervention strategies targeting ER dysfunction provide hope for future therapy and prevention.

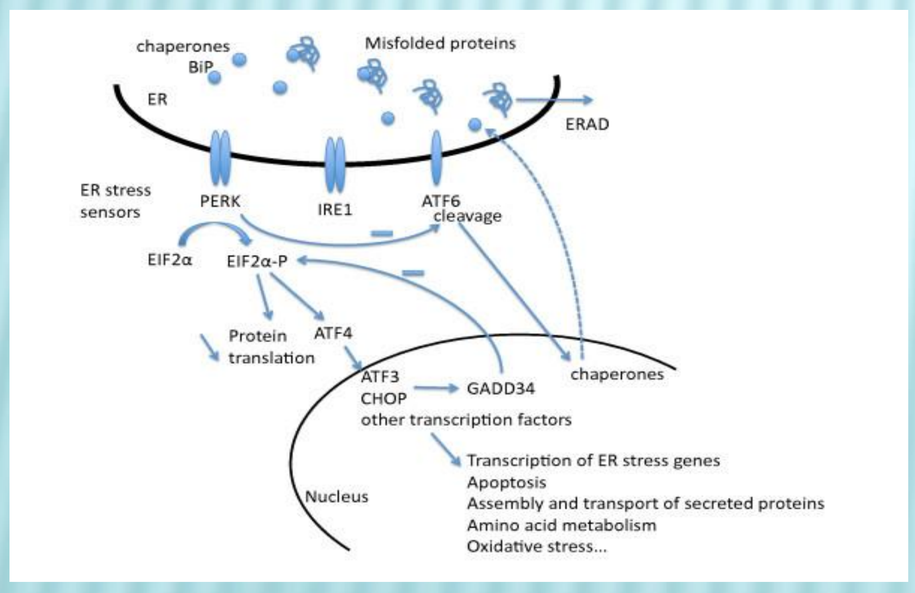


Fig. 3 Schematic representation of the main UPR mechanisms, focusing on PERK related pathways. Upon accumulation of misfolded proteins in the ER lumen, chaperones such as BiP are displaced from the ER stress sensors PERK, IRE1 and ATF6, resulting in their activation. Upon phospohorylation, PERK assembles in a homodimer (active form), which phosphorylates EIF2α, initiating the downstream UPR response, that reduces the protein overload to the ER: 1) reduction of protein translation and 2) activation of ATF4 and other transcription factors including ATF3 and CHOP, resulting in a variety of cellular and biological effects. ATF3 and CHOP are also involved in a regulatory feedback control of PERK-EIF2α dependent on GADD34. PERK also regulates ATF6, which induces the expression of chaperones, such as BiP and ERp72, which are essentiel in protein processing and quality control. Misfolded proteins are then dissociated by retrotranslocation to the cytosol and degradation by the ubiquitine/proteasome complex (ER associated degradation, or ERAD).

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