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MEHMO syndrome and the link between brain, pituitary and pancreas

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In 1998, Steinmuller et al. described a previously unrecognized syndrome featuring mental retardation, epileptic seizures, hypogonadism, microcephaly, and obesity (MEHMO syndrome; MIM 300148) and mapped the disease locus to Xp22.13-p21 [7]. Interestingly, in addition to the symptoms/signs included in the acronym MEHMO, the proband presented with non-autoimmune diabetes at the age of 6 months, a condition currently defined as neonatal diabetes [1]. Diabetes was not reported in the other three affected males of the family who died at 7, 2 and 10 months of age. Fourteen years later, Borck [2] identified a hemizygous missense mutation (p.Ile223Thr) in the eukaryotic translation initiation factor 2 subunit 3 (EIF2S3, or eIF2γ) in three males from a consanguineous family of Moroccan Jewish ancestry that disrupted EIF2 complex formation, resulting in defects in translation initiation, and MEHMO phenotype (Borck however did not associate the mutation with MEHMO syndrome.). Since then, *EIF2S3* mutations have been described including the Ile465Ser*fs 4 found in the original family reported by Steinmuller, and in two additional individuals with MEHMO and early-onset (<1 year of age), non-autoimmune diabetes [6]. Other two missense mutations, p.Ser108Arg and p.Ile259Met were detected in three patients all exhibiting the main features of MEHMO's phenotype, and other endocrine manifestations such as growth hormone deficiency (GHD) and hypoglycaemia [4].

A study published in the current issue of *EBioMedicine* has expanded the spectrum of EIF2S3 variants. It describes monozygotic twin brothers and their maternal cousin, born to a non-consanguineous white European pedigree, that presented with normal head circumferences, mild learning difficulties, severe recurrent hypoglycaemia, short stature with GHD, and thyrotropin (TSH) deficiency. There was also an unusual metabolic phenotype fluctuating between post-prandial hyperglycaemia and hyperinsulinaemic hypoglycaemia that remitted before puberty with persistence of glucose dysregulation characterized by post-prandial hyperglycaemia and variable, fasting hypoglycaemia [3]. Exome sequencing of the X chromosome revealed a novel hemizygous missense variant c.1294C > T in *EIF2S3* (p.Pro432Ser) in the three patients while the same change was found in their mother in heterozygous state.

To get a better insight of the effects determined by *EIF2S3*/Pro432Ser at the level of hypothalamic-pituitary and endocrine pancreas cells, several functional analyses were performed, including *in situ* hybridization on human embryonic tissues, EIF2S3-knockdown studies in the human hybrid pancreatic cell line 1.1B4 (coupled with an apoptosis assay), and the effect of humanized mutated protein on translational control in yeast.

In situ hybridization revealed that *EIF2S3* mRNA is strongly expressed in the pancreatic islet of 13 week-old human foetus, suggesting a role of eIF2γ in the developing endocrine pancreas. In addition, *EIF2S3* signal was detected in the hypothalamus, Rathke's pouch, anterior and posterior pituitary, and progenitor cells of the nasal epithelium and retina. 1.1B4 cell clones with reduced (82% reduction) *EIF2S3* gene expression, obtained by gene knockdown, was associated with enhanced caspase activity, suggesting that the decreased viability observed in these 1.1B4 cell clones is likely linked to apoptosis.

With an elegant experiment Authors show that yeast Pro490Ser mutation (corresponding to human eIF2γ/Pro432Ser) leads to a slight but measurable increase of GCN4 gene expression, with modestly impaired translational control and start codon selection stringency. In contrast, yeast mutation Ile318Met (corresponding to human mutation eIF2γ/Ile259Met, associated with “classic” MEHMO phenotype) [4] showed an extremely reduced eIF2γ function.

Overall, this data indicates that the *EIF2S3*/Pro432Ser mutation impacts moderately on eIF2γ functionality, and this may justify the departure from standard MEHMOs. features. In addition, the peculiar metabolic phenotype found in these three patients indicates that hypoglycaemia and non-autoimmune diabetes are frequent in MEHMO syndrome [8], maybe calling for a revision of the acronym.

In this report the authors demonstrate whole-exome sequencing as a successful approach to identify novel candidate genes underlying syndromic hypopituitarism associated with combined pituitary defects and pancreatic dysfunction. The insights provided by this study suggest that the Pro432Ser variant would cause a relatively mild phenotype of MEHMO syndrome compared to what was previously reported in the literature and have a role in the developing endocrine organs. Brain MRI in the three boys provided evidence of a small anterior pituitary with a normal posterior pituitary and stalk which is associated with

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GH and TSH deficiencies and supports the role of eIF2γ in hypothalamo-pituitary development and function. It also suggests an additional, important role of *EIF2S3* in the organization of central hormone secretion. Moreover, the high *EIF2S3* expression found in the developing endocrine pancreas, and the early presentation of hypoglycaemia and diabetes in most of MEHMO syndrome's patients suggests that eIF2γ may play a crucial role in glucose metabolism, like *EIF2AK3* in Wolcott-Rallison syndrome. Of note, *EIF2S3* is included in the panel of genes studied in patients with syndromic neonatal diabetes (https://www.diabetesgenes.org/tests-for-diabetes-subtypes/targeted-next-generation-sequencing-analysis-of-45-monogenic-diabetes-genes/). At this point in time however, the pathophysiology of hypoglycaemia in these patients is not clear. While hyperinsulinaemic hypoglycaemia can be observed in patients carrying *HNF4A* or *ABCC8* mutations who develop diabetes later in life [5,9], hyper- and hypoglycaemia coexist in individuals described in Gregory's paper in a way that resembles patients with mutations in the insulin receptor gene [10]. Further studies are needed to clarify this issue, including the impact of *EIF2S3* mutations on pancreatic α cell function and glucagon secretion.

MEHMO syndrome should be suspected early in male patients with a milder phenotype of learning difficulties, growth delay and hormonal deficiencies as well as glucose dysregulation. Timely diagnosis and treatment of hormone defects and hypoglycaemia may be critical for the prevention of significant neurodevelopmental delay.

Author disclosure

The authors declare no conflicts of interest.

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