Neonatal hypoglycemia, early-onset diabetes and hypopituitarism due to the mutation in *EIF2S3* gene causing MEHMO syndrome

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SUMMARY

Background: Recently, the genetic cause of several syndromic forms of glycemia dysregulation has been described. One of them, MEHMO syndrome, is a rare X-linked syndrome recently linked to the *EIF2S3* gene mutations. MEHMO is characterized by Mental retardation, Epilepsy, Hypogonadism/hypogenitalism, Microcephaly, and Obesity. Moreover, patients with MEHMO had also diabetes and endocrine phenotype, but detailed information is missing.

Aims and Patients: We aimed to provide more details on the endocrine phenotype in two previously reported male probands with MEHMO carrying a frame-shift mutation (I465fs) in the *EIF2S3* gene. **Results:** Both probands had a neonatal hypoglycemia, early onset insulin-dependent diabetes, and hypopituitarism due to dysregulation and gradual decline of peptide hormone secretion.

Conclusions: Based on the clinical course in our two probands and also in previously published patients, neonatal hypoglycemia followed by early-onset diabetes and hypopituitarism may be a consistent part of the MEHMO phenotype.

INTRODUCTION

Monogenic diabetes is a heterogeneous group of disorders caused by a mutation of a single gene involved to the insulin secretion or action (Rubio-Cabezas et al. 2014). The highest prevalence of monogenic diabetes is in patients with neonatal (<6 months) and infancy onset (<1 year) diabetes mellitus (Rubio-Cabezas et al. 2014; Stanik et al. 2007). There are several subtypes of monogenic neonatal and infancy onset diabetes, i.e. 1. disorders with abnormal pancreatic development including pancreatic agenesis and imprinting abnormalities, 2. disorders with abnormal β-cell function, particularly including *INS*, *KCNJ11*, and *ABCC8* mutations, and 3. disorders causing destruction of β-cells by dysfunction in the unfolded protein response pathway (Walter and Ron 2011; Wang and Kaufman 2012) including recently published Ile465Serfs mutation in the *EIF2S3* gene causing the MEHMO syndrome (Skopkova et al. 2017). The *EIF2S3* gene encodes the γ subunit of eukaryotic translation initiation factor 2 (eIF2), crucial for initiation of protein synthesis and regulation of the integrated stress response. MEHMO syndrome (OMIM# 300148) is characterized by X-linked intellectual disability, epileptic seizures, hypogonadism, hypogenitalism, microcephaly, and obesity (Leshinsky-Silver et al. 2002). Diabetes or endocrine phenotypes have not been included to the main signs of the MEHMO syndrome. Nevertheless, majority of the previously published MEHMO patients had hypoglycemia or diabetes and/or endocrine phenotype, but detailed information is missing. Therefore, we aimed to provide more details on the endocrine phenotype in two male probands with MEHMO carrying a frame-shift mutation (I465fs) in the *EIF2S3*gene (Skopkova et al. 2017).

PATIENTS AND METHODS

We refer on two probands with MEHMO syndrome of Slovak origin. Glucose, serum C-peptide, and hormone levels were measured in local labs by standardized methods. HbA1c was evaluated from whole blood by LPLC DiaSTAT analyzer (Bio-Rad). All steps of this study were approved

by the Faculty Hospital Ethics Committees in Bratislava. Parents of both patients had signed the informed consent.

RESULTS

Diabetes and endocrine phenotypes of the affected probands with MEHMO syndrome are summarized in Table 1.

Patient 1 (MEHMO syndrome with diabetes and panhypopituitarism)

The proband is a 2nd child of non-consanguineous parents of Slovak origin and the only male offspring in the mother´s family. His mother who carried the same *EIF2S3* gene mutation as her son had sideroblastic anaemia; father and older sister are healthy. The proband had prenatally diagnosed microcephaly at 28th week of gestation. He was delivered in 39+6 gestational week with birth length of 47 cm (-2.0 SDS) and weight 2920 g (-1.4 SDS) and head circumference 32 cm (-2.6 SDS). *Diagnosis of MEHMO* was made at the age of 10 months based on the microcephaly, unstable partial complex epileptic seizures resistant to anticonvulsives, hypogenitalism, severe mental and motor delay, central obesity, and typical dysmorphic features (for photo please see (Skopkova et al. 2017)). Currently he is 6 years old.

Glycemia and Diabetes phenotype. Hypoglycemia < 1 mmol/l firstly occurred at birth and was corrected with glucose infusion. Hypoglycemia (2.6 mmol/l) reoccurred at the age of 3 months when he was admitted to the hospital with lethargy, vomiting and hypotrophy (weight of 3830 g, -2.9 SDS). Insulin and C-peptide serum levels were in normal range (Table 1) at that time. Diabetes (2h oral glucose tolerance test glycemia 14 mmol/L; HbA1c 7.5 % (58 mmol/mol)) was diagnosed at the age of 10 months with mild polyuria but without ketoacidosis (pH 7.37, HCO3 26.1 mmol/l). Type 1 diabetes specific autoantibodies were negative. Fasting C-peptide was within normal range for normoglycemic subjects at the point of diagnosis, but decreased over the time (Table 1). The proband was treated by three daily doses with both regular and NPH insulin

injections since the age of 1 year. Despite intensive glycemic monitoring he had poor glycemic control with large glycemic excursions, particularly during respiratory infections. The proband was lethargic in euglyceamia and needed target glycemia levels between 10-15 mmol/l to be awake.

Endocrine phenotype. Panhypopituitarism with growth hormone deficiency, central hypothyroidism, central hypocorticism, low prolactin levels, and low gonadotropin levels with micropenis and cryptorchism was diagnosed at the age of 9 months. Since then he has been treated with substitution therapy of L-thyroxin and cortisol. Most of the peptide hormone levels decreased over the time (Table 1). The brain MRI at the age of 4 months showed a normally developed pituitary gland without any pathological changes. *Other features:* he suffers from recurrent respiratory tract infections.

Patient 2 (MEHMO syndrome with diabetes and partial hypopituitarism)

The 2nd proband is a 1st child of non-consanguineous parents of Slovak origin, and he was born in 40+0 gestational week with length of 49 cm (-0.95 SDS) and weight 2440 g (-2.65 SDS), and head circumference 29 cm (-5.1 SDS). *MEHMO features* were very similar to the 1st proband (Skopkova et al. 2017) including the unstable epileptic seizures resistant to anticonvulsives The proband inherited the *EIF2S3* gene mutation from his asymptomatic mother.

Glycemia and Diabetes phenotype. The second proband had also period of neonatal hypoglycemia corrected with glucose infusion. He was diagnosed with diabetes (fasting glycemia 14.7 mmol/l; HbA1c 8.7 % (72 mmol/mol)) at the age of 10 months without ketoacidosis. Type 1 diabetes specific autoantibodies were negative. Fasting C-peptide was within the normal range for normoglycemic subjects at the point of diagnosis, but decreased over the time. The proband was treated with three daily insulin injections (<0.3 U/kg/day), but did not achieve good glycemic control (Table 1).

Endocrine phenotype. Partial panhypopituitarism with growth hormone deficiency, low prolactin levels, low gonadotropin levels with micropenis and cryptorchism was diagnosed at the age of 9 months. The decline of peptide hormone levels with aging was similar to Patient 1(Table 1). The 2nd proband died at the age of 3.5 years because of infection and cardiorespiratory failure.

DISCUSSION

We reported on detailed diabetes and endocrine phenotype in two male probands with the MEHMO syndrome. Both patients developed non-autoimmune infant-onset diabetes with decline of endogenous insulin production with age. Moreover, one of them had decline also of all hypophyseal peptide hormones; the second proband had impaired growth, thyroidal, and prolactin axis (but not ACTH production). The decline of the peptide hormone levels could be explained by the severe impairment of protein synthesis caused by the causal Ile465Serfs mutation in the *EIF2S3* gene (Skopkova et al. 2017). All the patients carrying this mutation had similar phenotype including growth retardation and dysregulation of insulin secretion (Skopkova et al. 2017; Moortgat et al. 2016). In both our patients, neonatal hypoglycemia preceded diabetes onset later during the life. This is similar to congenital hyperinsulinism and maturity-onset diabetes caused by dysregulation of insulin secretion due to mutations in genes *HNF1A* and *HNF4A* (Stanescu et al. 2012; Rozenkova et al. 2015). Nevertheless, in case of MEHMO, also growth hormone deficiency could participate to the pathogenesis of hypoglycemia. Early-onset diabetes and endocrine symptomatology can also be seen in majority of other disorders caused by increased endoplasmic reticulum stress or a dysfunction in the unfolded protein response pathway, i.e. syndromic form of intellectual disability and diabetes caused by mutations in the *PPP1R15B* (Kernohan et al. 2015; Abdulkarim et al. 2015), Wolcott-Rallison syndrome caused by mutations of the *EIF2AK3* gene (Delepine et al. 2000), Wolfram syndrome caused by mutations in the *WFS1* gene (Fonseca et al. 2005), diabetes and multisystemic neurodegeneration caused by mutations of the *DNAJC3* (Synofzik et al. 2014), and Microcephaly, Epilepsy, and

Diabetes Syndrome (MEDS) caused by mutations of the *IER3IP1* gene (Abdel-Salam et al. 2012).

In conclusion, we reported on two patients with MEHMO syndrome with neonatal hypoglycemia followed by early onset diabetes, and hypopituitarism presumably due to dysregulation of protein synthesis and gradual decline of peptide hormone secretion. The genetic analysis of genes involved in protein translation and its regulation needs to be considered in patients with syndromic forms of diabetes and endocrine related syndromes.

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Contribution statement

All authors contributed to the study design and reviewed the manuscript critically and approved the final version. J.S. researched data and wrote the manuscript; M.S., D.S., K.B., L.B., L.T., J.H. and I.K. researched data, and M.S. and D.G. reviewed/edited the manuscript.

Conflict of interests: No potential conflict of interests.

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Table 1. Diabetes and endocrine phenotypes of two probands with MEHMO syndrome.

Abbreviations: DM (diabetes mellitus), HbA1c (glycosylated hemoglobin), oGTT (oral glucose tolerance test), IAA (insulin autoantibodies), I2-2A (tyrosine-phosphatase autoantibodies), GADA (glutamate-decarboxylase autoantibodies), ICA (islet autoantibodies), N (normal values), N/A (not analyzed), BMI (body mass index), SDS (standard deviation score), IGF1 (insulin-like growth factor 1), ACTH (adrenocorticotropic hormone), DHEAS (dehydroepiandrosterone sulfate), TSH (thyroid-stimulating hormone), fT4 (free thyroxine), TPO (thyroidal peroxidase), TG (thyreoglobulin), LH (luteinizing hormone), FSH (follicle-stimulating hormone). * on treatment. Blanks correspond to unavailable data.

Patient	**Proband 1**							**Proband 2**		
Time	prior DM diagnosis	at DM diagnosis	follow up 1	follow up 2	follow up 3	follow up 4	follow up 5	at DM diagnosis	follow up 1	follow up 2
Age	3 months	10 months	2 years	3 years	4 years	5 years	6 years	10 months	2 years	3 years
Glucose metabolism										
HbA1c, %/mmol/mol (N: 4.0-6.0/20-42)		7.5/58	8.1/65*	9.5/80*	9.3/80*	8.8/73*	9.0/74.9*	8.7/72	8.0/64*	8.1/65*
Glycemia, fasting, mmol/l (N: <5.6)	2.6	4.8	9.8*	12.6*	10.3*	13.9*	13.9*	14.70	4.7*	7.5*
C-peptide, fasting, pmol/l (N: 370-1470)	847	901	435*	379*	309*	347*	226*	696	439*	219*
Insulin, fasting, mU/l (N:2.6-24.9)	14.9 (in glycemia 5.5 mmol/L)	7.6	34.6*	29.9*	37.8*				8.5*	
Glycemia, 120 min oGTT, mmol/l (N: <7.8)		14								
C-peptide, 120 min oGTT, pmol/l		1556								
Insulin, 120 min oGTT, mU/l		20.2								
Glycemia, postprandial, mmol/l	4.5		18.1*	17						
Autoantibodies IAA, GADA, IA-2A, ICA		Negative	Negative					Negative		
Therapy: insulin, IU/kg/day	not treated	Diet	Insulin, 0.4	Insulin, 0.6	Insulin, 0.6	Insulin, 0.6	Insulin, 0.8	Insulin, 0.2	Insulin, 0.2	Insulin, 0.1
Growth										
Height, cm /SDS	55/-1.7	67.5/-1.6	74/-4.0	87/-2.4	87/-3.9	88/-4.9	90/-5.9	62/-3.4	71/-4.9	78/-4.7
Weight, kg	3.8	8.1	10.0	13.8	16.0	16.5	16.5	8.3	10.0	11.6
BMI, kg/m^2 / SDS	12.6/-2.2	17.8/0.7	18.3/1.5	18.2/1.5	21.1/2.7	21.3/2.7	20.4/2.2	21.6/2.9	19.8/2.3	19.1/1.9

IGF1 basal, ng/ml (N: 50-286)	<25	<25	<25	28.7	44.7			26.1	<25	
IGF1 peak in insulin test, ng/ml		<25								
Growth hormone basal, mIU/l	1.04	0.74			0.43					
Growth hormone peak in insulin test, mIU/l (N:>20)		1.14								
Growth hormone peak in clonidine test, mIU/l (N:>20)		1.08								
Growth hormone peak after 2h sleap, mIU/l (N:>20)		1.01								
ACTH and corticoids										
ACTH basal, pg/ml (N:7.2-63.3)	135	27.50	1.3*		<1.0*		13.3*	18.2		
Cortisole, basal, nmol/l (N: 171-536)	587.7	294.5	492.9*	376.7*	955.5*	360.5*	251.9*	539.3	443.9	
Cortisole, peak in insulin test, nmol/l		452.5								
Cortisole, peak in synacten test, nmol/l	1390									
DHEAS, µg/dl (N: 2.8-85.2)	69				0.1*				9.4	
Therapy: cortisol, mg/day	not treated	3	6	6	6	6	6	not treated	not treated	not treated
Thyroid										
TSH, mIU/l (N:0.8-6.9)	5.7	0.3*	0.32*	1.46*	0.46*	0.18*	0.31*	1.8	2	2.7
fT4, pmol/l, (N: 12.1-25.4)	9.7	16.9*	18.2*	15.7*	15.7*	16.5*	14.9*	11.1	17	11.6
Autoantibodies antiTPO, antiTG	Negative		Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Therapy: L-thyroxin, µg/day	not treated	19	19	20	19	19	19	not treated	not treated	not treated
Gonadotropins										
LH, IU/l (N:<4)		2		<0.1	<0.1			0.2	<0.1	
FSH, IU/l (N:<7.1)		1		0.8	0.9			0.7	0.3	
Testosterone, ng/ml (N:<0.025)	0.33			<0.025	<0.025					
Prolactine, ng/ml (N: 4-15.2)		4.6	2.5	1.4	1.1			3.1	1.4	