Genetic analysis and follow-up of 25 neonatal diabetes mellitus patients in China

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Objectives:

To study the clinical features, genetic etiology and the correlation between phenotype and genotype of neonatal diabetes mellitus (NDM) in Chinese patients.

Methods:

We reviewed the medical records of 25 NDM patients along with their follow-up details. Sanger sequencing of genes *KCNJ11* and *ABCC8* were performed in all NDM patients within first year after diagnosis, and if the mutations were not within the genes, gene panel-based next-generation sequencing (NGS) was used to detect mutations in PNDM, microarray comparative genomic hybridization was performed in TNDM patients to detect uniparental disomy of chromosome 6 (UPD6) and paternal 6q24 duplication. We called back KATP-PNDM patients and switched insulin injection to oral glyburide, usually it happened within one and half a year after diagnosis.
We selected 15 infantile onset T1DM patients who hospitalized at the same period (15 patients had recorded HbA1c in PNDM group) as control group, and HbA1c levels in these controls were compared with PNDM group.

Subtype	Gender	Term or preterm	HbA1c at diagnosis (%)	Age at last visit (yr)	HbA1c (%) at last visit	Height(cm) (percentile)	Weight(kg) (percentile)	Mutant gene	Inherited from		De novo mutation	Specific Clinical features	Mutation	zygosity	Insulin/Glyburide Therapy (age at transfer)
									father	mother					
PNDM	M	Term	13.7		6.1%	.0(P75)	.0(P50)	*KCNJ11*			p.R201H	Congenital cataract	c.602G>A;p.R201H	HET	Insulin/Interruption because of side effect(1yr)
PNDM	F	Term			6.0%	.0(P50-75)	.5(P50-75)	*KCNJ11*			p.R201H		c.602G>A;p.R201H	HET	Glyburide Response(0.7mg/kg/d)(3 months)
PNDM	M	Term	9.6		6.5%	.0(P25)	.0(P10-P25)	*KCNJ11*			p.G53S		c.157C>T; p.G53S	HET	Glyburide Response(0.4mg/kg/d)(7 months)
PNDM	M	Term	8.1		7.5%	.0 (P3)	.0(P3)	*KCNJ11*			p.V59M	iDEND	c.175G>A;p.V59M	HET	Glyburide Response(4 months)
PNDM	M	Term						*KCNJ11*		p.E229K			c.685G>A; p.E229K	HET	Insulin/No transition because of lost to follow up
PNDM	F	Term	9.6		8.0%	.0(P10)	.0(P3-10)	*ABCC8*		p.R825W			c.2473C>T; p.R825W	HET	Insulin/No response(4 months)
PNDM	F	Term				.0(P50-75)	.5(P25-50)	*INS*					c.293C>A;p.S98I	HET	Insulin
PNDM	F	Term	14.2					*GLIS3*	no sample	no sample		Died of liver and kidney failure at 1.5 yr of age	c.2570T>A; p.F857Y	HET	Insulin
PNDM	M	Term	10.4			.0(P25-P50)	.5(P10-P25)	*SLC19A2*	no sample	no sample		moderate normocytic anemia	c. 1213A>G;p.T405A	HET	Insulin
PNDM	M	Term	9.5		7.0%	.0(<P3)	.0(<P3)	*EIF2AK3*	p.C532STOP			Wolcott-Rallison syndrome	c.1798A>T; p.C532STOP	HET	Insulin
PNDM	F	Term				.3(<P3)	.0(<P3)	*EIF2AK3*	p.leu182leufsX19	p.Arg588Ter		Wolcott-Rallison syndrome	c.1762C>T,p.Arg588Ter; c.544delC,p.leu182leufsX19	HET	Insulin
PNDM	F	Term	9.8		7.5%	.0(P50)	.0(P10)								Insulin (0.8IU/kg/d)
PNDM	M	Term	15.8		7.9%	.5(P50-P75)	.0(P50)								Insulin (based on glucose, injection once every other day)
PNDM	M	Term	4.38			.0(<P3)	.0(<P3)					Died of DKA at 7 months of age, Intellectual and physical retardation			Insulin
PNDM	M	Term	5.2			.0(P25)	.5(P10-P25)								Insulin
PNDM	M	Term				.0(P75)	(P50-75)								Insulin
PNDM	M	Term	5.9			.0(P50-75)	.0(P90)								Insulin
PNDM	F	Term				.0(P75)	.0(P50)								Insulin
TNDM	F	Term	7.1	1.8				*ABCC8*		p.G296R			c.886G>A;p.G296R	HET	
TNDM	M	Term		1.8		.6(P25-50)	.2(P25-50)	*ABCC8*		p.D212E			c.636G>T;p.D212E	HET	
TNDM	F	Term	9.6		5.7%	.5(P25-50)	.0(P50)	UPD6							
TNDM	F	Term	7.4		5.6%	.0(P50)	.0(P75)								
TNDM	M	Term		5.5	5.6%	.5(P25-50)	.0(P10-25)								
TNDM	M	Term	9.9	3.7	5.2%	.3(P75)	.5(P50-75)								
TNDM	F	Term		4.0											

Results:

Of 25 NDM patients, 18 (72.0%) were PNDM and 7 (28.0%) were TNDM. Among 18 PNDM cases, 6 (33.3%) had known KATP channel mutations (KATP-PNDM), including one *ABCC8* and five *KCNJ11* gene mutations. There were six non-KATP mutations, five novel mutations, including *INS*, *EIF2AK3* (n=2), *GLIS3* and *SLC19A2*, one known *EIF2AK3* mutation. There are two *ABCC8* mutations in TNDM cases and one paternal UPD6q24. Five of the six KATP-PNDM patients were tried for glyburide transition, 3 were successfully switched to glyburide. Except three PNDM patients without recorded HbA1c, the mean HbA1c was 7.4% in 12 patients on insulin therapy, 6.8% in 3 patients switched to glyburide and 7.2% in 15 PNDM patients. Mean HbA1c of PNDM was not significantly different from infantile onset T1DM (7.2% vs 7.4, P=0.41).

Conclusions:

PNDM accounted for 72% of NDM patients. About one-third of PNDM and TNDM patients had KATP mutations. The genetic etiology could be determined in 50% of PNDM and 43% of TNDM cases. PNDM patients achieved good glycemic control whether on insulin or on glyburide therapy.

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