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MINI REVIEW

MNX1 mutations causing neonatal diabetes: Review of the literature and report of a case with extra-pancreatic congenital defects presenting in severe diabetic ketoacidosis

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ABSTRACT

The *MNX1* gene encodes a homeobox transcription factor found to be important for pancreatic beta cell differentiation and development. Mutations of the *MNX1* gene that cause permanent neonatal diabetes mellitus (PNDM) are rare and have been reported in only two cases. Both cases presented with hyperglycemia, with one case having isolated PNDM while the other had PNDM and multiple neurologic, skeletal, lung, and urologic congenital anomalies resulting in death in early infancy. We describe the genetic and clinical features of a preterm male infant with a homozygous [c.816C > A p.(Phe272Leu)] *MNX1* mutation. Our proband is the first case to present in severe diabetic ketoacidosis (DKA), indicating severe insulin deficiency. Unlike the previously reported female case who had the same mutation and presented with isolated PNDM, our proband had hypospadias and congenital umbilical hernia and showed poor growth on follow up. Our case suggests that *MNX1* mutations causing NDM can result in a range of extra-pancreatic features and a variable phenotype, similar to other transcription factors causing NDM such as *GATA6* and *GATA4* mutations. We also cannot exclude the possibility of sex-biased expression of *MNX1* gene (which was recently reported for other monogenic/neonatal diabetes genes such as the *NEUROD1* and *HNF4A* in humans) since the two male cases had associated multiple anomalies while the female case had isolated PNDM. Our report further defines the phenotype caused by recessive homozygous *MNX1* mutations and explores potential new mechanisms regulating *MNX1* gene expression which should be further explored.

INTRODUCTION

Neonatal diabetes mellitus (NDM) is a monogenic disorder with over 30 known genetic causes, each with a specific inheritance pattern, phenotype, and clinical features. Mutations in 14 transcription factor genes were reported to cause permanent neonatal diabetes mellitus (PNDM)[1]. The *MNX1* gene (Motor Neuron and Pancreas Homeobox 1) encodes a homeobox transcription factor that was found essential for the formation of the dorsal pancreatic bud (from which endocrine cells develop)[2], differentiation of its cells into beta cells and their proliferation[3]. It is also important for spinal cord motor neuron cell fate specification[4]. More than 30 pathogenic mutations of *MNX1* gene have been reported[5], the majority of which cause autosomal dominant Currarino syndrome. Heterozygous loss of function variants in *MNX1* cause Currarino syndrome, a rare congenital condition characterized by anorectal malformations with variable neurological, urogenital, and skeletal features. Two distinct homozygous recessive missense mutations have been reported to cause PNDM. One mutation [c.816C > A p.(Phe272Leu)] was reported to cause isolated PNDM with severe hyperglycemia but not ketoacidosis[6]. The other [c.744C > G p.(Phe248Leu)] was reported to cause mild diabetes and severe congenital anomalies (neurodevelopmental, skeletal, urogenital,

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sacral, lung) with death early in life[7]. We report a third case that broadens the clinical spectrum of recessive *MNX1* mutation presentations; a case of an infant with a homozygous *MNX1* mutation [c.816C > A p.(Phe272Leu)] presenting with severe hyperglycemia in severe diabetic ketoacidosis, with extra-pancreatic features poor growth in height; we review the literature comparing cases with the *MNX1* mutation causing diabetes.

PATIENT AND METHODS

Our proband is the second born child of first cousin consanguineous parents. There is no known family history of diabetes. He has two healthy siblings (a brother and a sister). He was born by cesarean section at 36 weeks gestation due to premature labor with fetal heart deceleration. The birth weight was 1.7 kg. He had hypospadias and an umbilical hernia. He was not hospitalized for being IUGR. No data are available about his height at birth but his blood sugar at birth was checked and was within the normal range. He continued to show poor weight gain after birth despite good feeding.

At 21 days of age, he developed a marked increase in the frequency of feeding, leaking diapers despite more frequent diaper change together with weight loss and excessive crying. Within a few days, he started to vomit and developed respiratory distress.

On presentation, he weighed 1.35 kg (below 5th percentile). He was tachypneic with evident Kussmaul's breathing.

He was in diabetic ketoacidosis: the blood glucose (BG) was 630 mg/dL, with ketonuria +++. Venous blood gas analysis showed pH = 6.9, pCO_2 = 19 mmHg, bicarbonate = 4 mmoL/L, anion gap = 24 meq/L. His C-peptide was <0.2 ng/mL (1.1–4.4).

The sepsis workup showed negative CRP, and no growth in blood and urine culture.

Echocardiography, abdominal ultrasound, and the skeletal survey were normal.

Management of diabetic ketoacidosis followed the International Society of Pediatric and Adolescent Diabetes guideline. On shifting to subcutaneous insulin, NPH insulin was initially used on 8-hourly divided small doses together with insulin lispro given with every other breast feed as needed. Adjustments of insulin doses were done based on the blood glucose readings. He showed adequate weight gain and was discharged after 3 weeks weighing 3.850 kg. A shift was made later to insulin glargine together with insulin lispro.

At age 6 months, he had surgical repair of hypospadias.

He is now 35 months old and is on 0.8 U/kg/day of insulin degludec 100 with mealtime Lispro. The last HbA1c was 8%. Before receiving the genetic testing result, a trial of oral sulphonylurea (gliclazide) was carried out but it failed, despite reaching a dose of 1.2 mg/kg/day and the patient remained insulin-dependent.

His height is 89 cm (at the 5th percentile for age), and he weighs 13.5 kg (between 25th–50th percentile for age). His father's height is between 25th and 50th percentile while mother's height is at the 90th percentile. His mid-parental height would put him at the 75th percentile for height.

His congenital umbilical hernia has shown regression in size over these 3 years.

Samples and mutation analysis

Parental informed consent to do genetic testing at Exeter University Medical School Genomics Laboratory, UK was obtained when the patient was 5 months old.

Leukocyte DNA was extracted and tested first for common causes of neonatal diabetes mellitus (mutations in the *ABCC8*, *KCNJ11*, and *INS* genes) by Sanger sequencing. No mutation was identified. Targeted next generation sequencing for mutations in all known NDM genes was then performed[8]. Genes analyzed included: *ABCC8*, *AGPAT2*, *BSCL2*, *CISD2*, *COQ2*, *COQ9*, *EIF2S3*, *EIF2B1*, *EIF2AK3*, *FOXP3*, *GATA4*, *GATA6*, *GCK*, *GLIS3*, *HNF1B*, *IER3IP1*, *IL2RA*, *INS*, *INSR*, *KCNJ11*, *LPL*, *LRBA*, *MNX1 exon 2*, *NEUROD1*, *NEUROG3*, *NKX2-2*, *PDX1*, *PTF1A*, *RFX6*, *SLC2A2*, *SLC19A2*, *STAT3*, *WFS1*, *YIPF5*, and *ZFP57*.

Our proband was found to be homozygous for a pathogenic *MNX1* missense variant [NM_005515.3: c.816C > A p.(Phe272-Leu)]. The mutation is located on Chr7: g.156799209.

Both parents are heterozygous carriers. Testing was not carried out for the siblings.

Literature review and discussion

Homozygous *MNX1* mutations causing NDM are rare and were previously reported in two cases[6,7]. The first report was in an Egyptian girl in France[6]. Our proband's mutation was reported in one of them (case 1, a female). Table 1 shows their characteristics.

All three cases were born with intrauterine growth retardation, indicating severe deficiency of insulin secretion *in utero*. Our proband continued to show severe failure to thrive until diagnosis and initiation of insulin, indicating a possible delay in the diagnosis of diabetes. Physician awareness of poor weight gain/weight loss as a main early presenting symptom of diabetes would help in the early diagnosis of diabetes and initiation of treatment.

Our proband was born preterm (36 weeks) while cases 1 and 2 were born at term (38, 40 weeks, respectively). Earlier work from Exeter, UK that examined 750 NDM cases from an international cohort showed that being preterm should not exclude the possibility of a genetic form of NDM as a cause of hyperglycemia since almost one-fifth (19.4%) of NDM patients were born preterm[9]. Thus, besides major causes of hyperglycemia in preterm infants such as prematurity and sepsis, NDM should not be missed as a possible cause.

Diabetes presentation was variable in the three patients. Cases 1 and 3 were diagnosed at a comparable age (17 and 21 days of age, respectively), with severe hyperglycemia (BG of 700 mg/dL and 630 mg/dL, respectively). However, only case 3 presented in diabetic ketoacidosis (pH = 6.9,

Table 1 | Characteristics of cases reported with *MNX1* mutations causing NDM and our patient

Characteristic	Bonnefond *et al.*[6] proband, Flanagan *et al.*[7] proband (case 1)	Flanagan *et al.*[7] proband (case 2)	Our proband (case 3)
MNX1 mutation	NM 005515.3: c.816C > A/ p.(Phe272Leu)	NM_005515.3: c.744C > G/ p.(Phe248Leu)	NM_005515.3: c.816C > A/ p.(Phe272Leu)
Gender	Female	Male	Male
Gestational age (weeks)	38	40	36
Weight at birth (kg)	1.9	2.23	1.7
SDS for gestational age and sex	−3.09	−2.54	−2.34
Age at diagnosis	17 days	30 weeks	21 days
BG at diagnosis (mg/dL)	700	218	630
pH at diagnosis	7.3	Not reported	6.9
Urine ketones at diagnosis	+	Not reported	+++
Diabetes auto-antibodies	none	Not reported	Not done
C-peptide (ng/mL)	Not reported	Not reported	<0.2
Insulin dose (U/kg/day)	0.8	0.3	0.8
HbA1c (%)	7.8	6.6	8
Reported age at last examination	36 months	Died at 10 months	35 months
Height at last examination	Normal stature (59th percentile)	Short stature (<5th percentile)	89 cm (at the 5th percentile for age)
Weight at last examination	11.7 kg, 10th percentile	Not reported	13.5 kg (is between 25th–50th percentile)
Pancreatic exocrine dysfunction	No	No	No
Extra-pancreatic anomalies	None	Neuro-developmental delay, skeletal deformities, sacral agenesis, poorly developed kidney, neurogenic bladder, imperforate anus, hypoplastic lungs, and short stature	Hypospadias, congenital umbilical Hernia

bicarbonate = 4.5 meq/L). Case 1 did not develop DKA over the 3-year period of follow up. Case 2 presented at a later age (30 weeks) with a much milder hyperglycemia (BG = 218 mg/dL). Both cases 1 and 3 needed insulin at 0.8 U/kg/day, while case 2 needed insulin at a lower dose of 0.3 U/kg/day.

The presentation of our proband in DKA, is a major difference from the other cases. Our proband had very low C-peptide (<0.2 ng/mL). Autoantibodies were not done as the presentation of these three cases was in the early neonatal period, and type 1 diabetes is extremely rare among individuals developing diabetes in the neonatal period. Our proband presentation was consistent with ketosis-prone diabetes (KPD) with poor pancreatic beta cell functional reserve.

Diabetic ketoacidosis is a serious acute complication of diabetes mellitus that can be fatal. It occurs in the setting of severe deficiency of required insulin. So far it has been reported with certain types of PNDM, which include: neonates with *KCNJ11*/*ABCC8* mutations, mutations of the insulin (INS) gene, and with mitochondrial diabetes[10,11]. Here we add to the list homozygous *MNX1* gene mutation [c.816C > A/p.(Phe272-Leu)].

A recent review of diabetes mellitus classification suggested the term KPD and its subclassification, based on the presence or absence of autoantibodies (A+ or A-) and beta-cell functional reserve as determined by the C-peptide level (β + or β-), account for the heterogeneity among different types of diabetes[12]. KPD is a heterogenous group of diabetes mellitus types characterized by presentation with DKA or unprovoked ketosis; they do not necessarily have the phenotype of autoimmune type 1 diabetes. A pilot study showed that approximately one quarter (27%) of A-β- patients have pathogenic mutations of the critical transcription factors needed for beta cell development causing monogenic diabetes (examples include mutations in genes encoding *HNF-1A* and *PDX-1*)[13]. Our proband classifies as having A-β- KPD, and *MNX1* mutation would be another example.

Development of diabetic ketoacidosis at presentation of our proband raises the question as to the severity of the beta cell defects caused by different *MNX1* mutations and factors regulating its expression since cases 1 and 3 have the same mutation.

A-β- patients are insulin-dependent. Our proband did not respond to sulphonylurea. As *MNX1* was found to be an essential transcription factor for the differentiation and proliferation of endocrine pancreatic cells, this explains his insulin-dependent diabetes phenotype. Inactivating mutations of *MNX1* gene were found to cause delta instead of beta cell fate in mouse pancreatic embryonic cells[14]. Both of our proband parents are heterozygous carriers indicating that one copy of the gene is enough for adequate beta cell function.

Moreover, case 1 did not have any extra-pancreatic anomalies. Case 2 had severe extra-pancreatic anomalies (Table 1) resulting in death at age 10 months. He had two of the major features of Currarino syndrome (sacral agenesis and imperforate anus), which is caused by heterozygous loss of function *MNX1* mutations and diabetes is not a feature of Currarino syndrome[15]. Our proband had extra-pancreatic anomalies in the form of hypospadias and congenital umbilical hernia. The common thought that females (such as case 1 who has the same mutation as our proband) do not get hypospadias is incorrect. Female hypospadias is described when the external urethral meatus opens high up in the anterior vaginal wall near the hymenal ring. It is a rare congenital anomaly that results from abnormal urogenital sinus development and is usually associated with other urogenital anomalies[16]. If diagnosis is missed, females present with incontinence (primary) and recurrent UTI with its complications[16]. *MNX1* gene is known to be located within a locus which was previously associated with hypospadias (a novel hypospadias locus was described at chromosome 7 (7q32.2-q36.1), the same chromosome carrying the *MNX1* gene[17]). None of the cases had exocrine pancreatic dysfunction.

The effect of *MNX1* recessive mutation on growth in the three cases was also variable (Table 1). While case 1 had a good height but a low weight at age 3 years, our patient had a height at the 5th percentile with an average weight at around 3 years age. Case 2 had very poor height falling below the 5th percentile. Given the height of both of our proband's parents, his growth is falling below his expected curve on the height percentile chart. Once the blood glucose is better controlled, and with further follow up of his height, if his gain in height is still poor, an assessment shall be done for the possibility of associated growth hormone deficiency.

A recent expert review on neonatal diabetes, stated that it is still unclear whether recessive *MNX1* mutations cause isolated or syndromic PNDM or both, since only two cases have been reported and that it would be essential to look for more cases to define its clinical phenotype[18]. Here we report the third case, it had syndromic PNDM, with a DKA presentation at onset together with urogenital anomaly (hypospadias) and congenital umbilical hernia.

The variable phenotype expression of the same genotype could be attributed to different genetic/epigenetic factors (e.g. modifier genes), or gene-by-environment interactions[19].

Variable presentation of both pancreatic and extra-pancreatic phenotype expression of the same genotype was reported with some of the other transcription factors that cause NDM such as *GATA6*, *GATA4*, and *PDX-1* mutations. *GATA6* haploinsufficiency[20–22] and *GATA4* mutations[23] were reported to result in a wide phenotypic spectrum of diabetes (from PNDM to adult-onset diabetes), exocrine pancreatic affection, and variable heart defects in individuals carrying the same mutation. There are also few reports of variable presentation of diabetes in patients carrying the exact same *PDX-1* genotypic mutation (from early-onset MODY 4 diabetes, gestational diabetes progressing to type 2 diabetes, or later-onset MODY-diabetes)[24,25]. Interestingly, the two male cases with *MNX1* mutations causing diabetes had a syndromic presentation whereas the female case had isolated PNDM. Recent research published in *Science* from the genotype-tissue expression project showed that sex-biased gene expression of transcription factors exists across different tissues (pancreas was one main tissue) causing sex-differentiated phenotypes and that it affects genes involved in hormone response[26]. Among the studied pancreatic genes that showed male-biased expression were *NEUROD1* and *HNF4A*, which are among known monogenic and neonatal diabetes genes[12,26].

Another recent report found sex-biased beta cell dysfunction in mice with the *MAFA* p.Ser64Phe missense mutation with only males showing impaired glucose tolerance and premature senescence[27]. The human *MAFA* gene encodes a transcription factor which activates insulin gene expression and can cause adult-onset diabetes[28].

Consistent with possible sex-biased expression of *MNX1* some reports from China and Korea of Currarino syndrome, which is caused by dominant *MNX1* mutations different from those that cause NDM, reported higher disease detection among females[29].

The identification of additional patients with NDM caused by *MNX1* mutations will be crucial to characterize the different phenotypes and to assess the possible mechanisms that result in the phenotype differences observed.

Moreover, the parents of our proband as well as the other reported cases, who had a heterozygous mutation, did not have features of Currarino syndrome. One possible explanation is that the two recessive missense variants causing NDM identified so far (the p.Phe248Leu and p.Phe272Leu) do not result in a complete loss of *MNX1* function, but only affect some of the *MNX1* functions, including beta cell development. This is also supported by the fact that these variants have not been identified in individuals with Currarino syndrome. The two variants affect a conserved residue within the homeobox domain of the *MNX1* protein, so they are likely to affect DNA binding to specific targets, i.e. position of mutant amino acid is likely relevant. Additional studies will be needed to clarify the difference in the mode of inheritance and phenotype caused by different *MNX1* mutations.

Both cases 1 and 3 are Egyptians, indicating the need for more collaborative studies to analyze NDM genetics in Egypt, to explore the possibility that this could be a founder mutation and the possible role of ethnicity on phenotype expression.

In conclusion, we report a case of a preterm male infant with the rare homozygous *MNX1* mutation [p.(Phe272Leu)] and describe the novel presenting features of the case. Our patient presented in severe diabetic ketoacidosis, had hypospadias and congenital umbilical hernia and showed poor growth on follow up. He remained insulin-dependent and failed to respond to sulphonylureas. As more cases are reported and with further studies elucidating the mechanisms regulating *MNX1* gene expression, better understanding of the role of this transcription

factor in human beta cell development can be gained allowing for further progress in diabetes regenerative therapies.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This case report is based on the result of genetic analysis of the proband who presented with neonatal diabetes. The parents' written consent to do the genetic analysis was sent to Exeter University Genomics Lab (Dr Elisa De Franco) with the blood samples. The parents also gave their written consent to publish the clinical and genetic features of this case. Institutional ethics approval is exempt for such cases.

Registry and the registration no. of the study/trial: Thus, approval date of Registry and the Registration No. of the study/trial: N/A (as stated above).

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

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