Growth and development in monogenic forms of neonatal diabetes

Batoul Hammoud and Siri Atma W. Greeley

Purpose of review
Neonatal diabetes mellitus (NDM) is a rare disorder in which 80–85% of infants diagnosed under 6 months of age will be found to have an underlying monogenic cause. This review will summarize what is known about growth and neurodevelopmental difficulties among individuals with various forms of NDM.

Recent findings
Patients with NDM often have intrauterine growth restriction and/or low birth weight because of insulin deficiency *in utero* and the severity and likelihood of ongoing growth concerns after birth depends on the specific cause. A growing list of rare recessive causes of NDM are associated with neurodevelopmental and/or growth problems that can either be related to direct gene effects on brain development, or may be related to a variety of co-morbidities. The most common form of NDM results in spectrum of neurological disability due to expression of mutated KATP channels throughout the brain.

Summary
Monogenic causes of neonatal diabetes are characterized by variable degree of restriction of growth *in utero* because of deficiency of insulin that depends on the specific gene cause. Many forms also include a spectrum of neurodevelopmental disability because of mutation-related effects on brain development. Longer term study is needed to clarify longitudinal effects on growth into adulthood.

Keywords
growth, insulin deficiency, monogenic diabetes, neonatal diabetes, neurodevelopmental delay

INTRODUCTION

Neonatal diabetes mellitus (NDM) is a rare disorder for which several studies support an incidence in the range of 1 : 90 000–160 000 [1]. Patients present during infancy with clinically significant persistent hyperglycemia (blood glucoses generally greater than 250 mg/dl) without alternative cause and that requires treatment [2]. Although type 1 and type 2 diabetes are polygenic disorders, several large international cohort studies have found that 80–85% of patients diagnosed with diabetes under 6 months of age have highly penetrant variants in 1 of almost 30 genes now identified. Mutations in these genes are most often sporadic but may be inherited in an autosomal dominant fashion, although many of the genes are associated with rare recessive forms of neonatal diabetes. Nearly all forms involve beta-cell insufficiency that may be because of a disruption of development or progressive destruction, as well as impaired insulin secretion and/or action [3].

Recent studies suggest that a small fraction of patients diagnosed under 6 months may actually have autoimmune type 1 diabetes rather than a monogenic cause [4], whereas after 6 months of age, the majority of patients will have autoimmune diabetes and only rarely will patients be found to have a monogenic form of diabetes [5]. Unlike other types of diabetes occurring at later ages, the cardinal signs of diabetes (polyuria, polydipsia) are very difficult to recognize and can be falsely reassuring in infants; consequently, these patients may experience a delay in diabetes diagnosis, with one United States study showing that two-thirds of neonatal diabetes patients had diabetic ketoacidosis at the time of presentation [6].

Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, and Kovler Diabetes Center, University of Chicago, Chicago, Illinois, USA

Correspondence to Siri Atma W. Greeley, Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism and Kovler Diabetes Center, The University of Chicago, 900 East 57th Street, Chicago, IL 60637, USA. E-mail: sgreeley@uchicago.edu

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KEY POINTS

- Most forms of neonatal diabetes are characterized by a variable degree of low birth weight that depends on the specific cause, reflecting the role of insulin as a growth factor *in utero*.
- KATP-related NDM is characterized by a spectrum of neurodevelopmental difficulties that is highly dependent on the specific mutation.
- Rare recessive causes will often have severely low birth weights as well as other syndromic features that sometimes includes severe brain malformations.
- Causes involving pancreatic agenesis or hypoplasia are also characterized by pancreatic exocrine insufficiency that results in frequent failure-to-thrive and longer term growth concerns.
- Monogenic causes of autoimmune diabetes often involve other autoimmune conditions, such as enteropathy that often lead to ongoing growth difficulties as well as short stature.

The most common causes of neonatal diabetes are because of activating heterozygous mutations in either of the two genes encoding subunits of the pancreatic beta-cell KATP channel (*KCNJ11* and *ABCC8*), or mutations in insulin gene (*INS*) itself. Phenotypically, neonatal diabetes may be transient but the majority of causes lead to permanent neonatal diabetes. Transient neonatal diabetes is most often because of overexpression of genes at chromosome 6q24 but can also be because of mild KATP mutations. Although patients with transient forms of neonatal diabetes will experience a remission of their diabetes usually within the first few months of life, an uncertain but high percentage of these patients will have recurrence of the diabetes later in life, usually in adolescence or young adulthood. Due to a diminished availability of insulin, all forms of neonatal diabetes are associated with a variable degree of growth restriction that may be apparent prenatally and/or postnatally. In addition, many forms of neonatal diabetes are also associated with a spectrum of neurodevelopmental disability that in most cases is thought to be because of extra-pancreatic manifestations of the underlying gene disorder rather than a result of the diabetes. Of note, the more common MODY forms of monogenic diabetes are typically diagnosed in adolescence and young adulthood, when growth and development are already reaching maturity; therefore, for this review, we will restrict the discussion to neonatal forms of monogenic diabetes, where most forms are associated with significant effects on growth and/or development.

INSULIN AS A GROWTH FACTOR *IN UTERO*

A majority of individuals with most forms of neonatal diabetes will have a history of intrauterine growth restriction (IUGR) or low birth weight, described as small for gestational age (SGA), which is thought to be because of insulin deficiency *in utero* [7]. Growth is governed by a complex network of endocrine signals and is related to nutrient availability [8]. Multiple studies have shown that longitudinal growth is impaired in children with diabetes [9–11], with some having described catch-up growth when those with poorly controlled diabetes achieve improved glycemia [12,13].

The effects of monogenic diabetes on growth have not yet been well studied in a longitudinal fashion but early consequences are apparent in those with neonatal forms of monogenic diabetes.

Fetal insulin secretion is a key growth factor, especially in the third trimester when the weight of the fetus increases greatly. Insulin stimulates fetal growth by increasing the mitotic drive and nutrient availability for tissue accretion [14]. Insulin deficiency in fetal sheep reduces growth rate by 50–60% during the last 30 days of gestation [15]. Clear clinical evidence of the role of insulin in human fetal growth is newborn macrosomia associated with diabetes in pregnancy that was proposed by Pedersen [16] in the 1950s to be a consequence not of increased glucose but rather by higher fetal insulin secreted in response to maternal hyperglycemia. Maintaining euglycemia (and consequent fetal production of insulin) in pregnancy lowers the risk of macrosomia [17]. It has been shown that a subset of macrosomic infants born to mothers without diabetes have higher insulin levels in cord blood [18].

It is, therefore, not surprising that most patients with all forms of neonatal diabetes will have low birth weight, and in those more severely affected, there will often be concerns about fetal growth during the pregnancy, especially in the third trimester (Table 1).

The prenatal and postnatal growth was followed in 49 patients with KCNJ11 mutations. Birth weight SDS (Standard deviation score) was greatly reduced −1.73 (−3.68 to 1.41) but there was significant postnatal catch-up soon after initiation of insulin, and normalization to population levels occurring by 9–12 months of age. Interestingly, severity of low birth weight did not correlate with severity of mutation (by in-vitro studies); however, those with the most severe neurological phenotype (developmental delay, epilepsy and neonatal diabetes, or DEND syndrome) were the only group who did not exhibit significant catch-up growth [19]. This study also

Table 1. Growth and development concerns for monogenic causes of neonatal diabetes

Gene	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas/ exocrine function	IUGR concerns	SGA	Growth and neurodevelopmental concerns, or other features
Most common causes of neonatal diabetes							
PLAGL1 *HYMAI* or *ZFP57* (6q24)	TNDM	UPD6 (40%; de-novo, nonrecurrent), paternal duplication (40%, may be inherited) or maternal methylation defect (20%; autosomal recessive, e.g. *ZFP57*)	Within days of life; remission within months; relapse during adolescence	Normal/ normal	Usually	Severe	Very SGA; macroglossia and/or umbilical hernia often present; other features may be seen in those with HIL, especially *ZFP57* mutations: variable developmental delay (6/9); CHD (3/9); visual impairment (3/9); epilepsy (2/9)
KCNJ11	PNDM (more often) or TNDM (less often); DEND	Spontaneous (80%) or autosomal dominant	<6 months; rarely later	Normal/ normal	Rarely	Mild	Mild-severe neurodevelopmental dysfunction is common; diabetes usually responsive to sulfonylurea therapy
ABCC8	PNDM (less often) or TNDM (more often); DEND	Spontaneous (80%) or autosomal dominant	<6 months; rarely later	Normal/ normal	Rarely	Mild	Often SGA; usually responsive to sulfonylurea therapy
INS	PNDM (more often), TNDM (rarely), MODY (rarely)	Spontaneous (80%), autosomal dominant or recessive (rarely)	<6 months; less often later	Normal/ normal	Rarely	Mild	Often SGA; rare later-onset patients with a MODY or antibody-negative phenotype
EIF2AK3	Wolcott–Rallison syndrome (WRS)	Autosomal recessive (most common recessive cause)	Usually within weeks; sometimes months	Rare hypoplasia/ often reduced (25%)	Sometimes	Variable	Mild SGA or normal, rarely very SGA; developmental delay (60–80%); epiphyseal dysplasia (90–100%); acute liver failure (60–75%); hypothyroidism (~25%); exocrine pancreatic dysfunction (~25%)
Causes involving pancreatic agenesis or significant hypoplasia							

Table 1 (*Continued*)

Gene	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas/ exocrine function	IUGR concerns	SGA	Growth and neurodevelopmental concerns, or other features
GATA6	PNDM, occasionally later-onset	Autosomal dominant	Usually days, rarely later	Agenesis or hypoplasia/ reduced	Often	Moderate-Severe	SGA/growth concerns; variable developmental delay; CHD (frequent); intestinal malformations; thyroid dysfunction; hepatobiliary defects
GATA4	PNDM	Autosomal dominant	Days, sometimes later	Agenesis or hypoplasia/ normal or reduced	Often	Moderate-Severe	SGA/growth concerns; CHD; intestinal malformations
PDX1	PNDM with pancreatic agenesis/hypoplasia	Autosomal recessive	Within days	Usually absent or small/ deficient or reduced	Often	Severe	SGA; diarrhea; malnutrition; parents may have *PDX1* MODY (MODY4)
PTF1A	PNDM with cerebellar and pancreatic agenesis	Autosomal recessive	Within days	Absent/absent	Often	Severe	Very SGA; cerebellar agenesis; flexion contractures; poor subcutaneous fat; optic nerve hypoplasia; detectable C-peptide/ insulin
Rare recessive causes often involving significant IUGR and/or SGA							
GCK	PNDM; GCK-MODY	Autosomal recessive	Within days	Normal/ normal	Sometimes	Moderate-severe	Very SGA, heterozygous parents have impaired fasting glucose with GCK-MODY (MODY2)
NEUROD1	PNDM with cerebellar (but not pancreatic) hypoplasia	Autosomal recessive	Within weeks	Normal/ normal	Often	Severe	SGA; severe cerebellar hypoplasia; moderate-to-severe developmental delay; sensorineural deafness; visual impairment; Heterozygous parents may have a MODY-like phenotype

Table 1 (*Continued*)

Gene	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas/ exocrine function	IUGR concerns	SGA	Growth and neurodevelopmental concerns, or other features
MNX1	PNDM	Autosomal recessive	Within weeks	Normal/ normal	Often	Severe	SGA/growth concerns; short stature; brain malformations; developmental delay; intestinal malformations; lung hypoplasia;
NKX2–2	PNDM	Autosomal recessive	Within days	Normal/ normal	Often	Severe	SGA/growth concerns; short stature; brain malformations; developmental delay; hearing impairment; eye malformations/blindness
NEUROG3	PNDM with severe congenital diarrhea	Autosomal recessive	Often within days, sometimes later	Small/normal	Often	Severe	Very SGA; severe intractable congenital diarrhea unresponsive to pancreatic enzyme replacement with absent intestinal enteroendocrine cells; hypogonadotropic hypogonadism; short stature
RFX6	PNDM with intestinal atresia, gall bladder hypoplasia	Autosomal recessive	Within days	Small/normal	Often	Severe	Very SGA; intestinal atresias; gall bladder hypoplasia/aplasia; diarrhea; parents may have MODY-like phenotype
IER3IP1	PNDM with microcephaly	Autosomal recessive	Usually within days	Normal/ normal	Often	Mild	Microcephaly with simplified gyral pattern; severe infantile epileptic encephalopathy

Table 1 (*Continued*)

Gene	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas/ exocrine function	IUGR concerns	SGA	Growth and neurodevelopmental concerns, or other features
HNF1B	TNDM/PNDM; (RCAD; MODY5)	Spontaneous or autosomal dominant	Within weeks	Hypoplastic/ reduced	Sometimes	Severe	Very SGA; renal abnormalities; relapsing/remitting DM (RCAD: renal cysts, urogenital abnormalities)
GLIS3	Neonatal diabetes with congenital hypothyroidism (NDH)	Autosomal recessive	Within days	Small, normal or cystic/ normal or reduced	Often	Moderate	SGA; congenital primary hypothyroidism; glaucoma (4/8); liver fibrosis (5/8); cystic kidney disease (4/8); osteopenia (1/8); deafness (1/8); facial dysmorphism
PAX6	PNDM with severe microcephaly and eye defects	Autosomal recessive	Within days	Normal/not reported	Often	Variable	Brain malformations; microcephaly; micropthalmia; panhypopituitarism; heterozygotes have mild eye defects, with occasional late-onset diabetes
WFS1	Wolfram syndrome; DIDMOAD	Autosomal recessive (most often)	Usually years, sometimes weeks	Normal/ normal	Rarely	Mild-normal	Optic atrophy (earliest feature); diabetes insipidus; deafness; cataracts; hypotonia
SLC19A2	Thiamine-responsive megaloblastic anemia (TRMA) syndrome	Autosomal recessive	Within months	Normal/ normal	Rarely	Variable	Thiamine-responsive megaloblastic anemia; sensorineural deafness; occasional CHD (conduction defects); short stature
SLC2A2	Fanconi Bickel syndrome (FBS)	Autosomal recessive	Usually within days or weeks	Normal/ normal	Sometimes	Variable	Hepatomegaly related to hepatorenal glycogen accumulation; proximal tubular nephropathy with glucosuria and hypophosphatemic rickets; glucose intolerance or diabetes; galactosemia,

Table 1 (*Continued*)

Gene	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas/ exocrine function	IUGR concerns	SGA	Growth and neurodevelopmental concerns, or other features
Monogenic causes of autoimmune diabetes occurring in infancy along with other autoimmune dyfunction							
FOXP3	Immunodysregulation polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	X-linked recessive	Days to months	Normal/ normal	Sometimes	Variable	Only males affected; severe immune dysregulation; chronic diarrhea with villus atrophy (95%); pancreatic and thyroid autoantibodies (75%); thyroiditis (20%); eczema (50%); anemia (30%); often die before 1 year without stem cell transplant
LRBA	PNDM, polyautoimmunity	Autosomal recessive	Weeks to months	Normal/ normal	Rarely	Mild-normal	Other autoimmune conditions in addition to diabetes; may have severe clinical picture (similar to IPEX) with consideration of immunomodulatory agents and/or stem cell transplant; significant risk for failure to thrive and short stature
IL2RA	PNDM, polyautoimmunity	Autosomal recessive	Within weeks	Normal/normal	Rarely	Mild-normal	
STAT1	PNDM, polyautoimmunity	Autosomal dominant	Months to 5 years	Normal/normal	Rarely	Mild-normal	
STAT3	PNDM, polyautoimmunity	Autosomal dominant	Within weeks	Normal/normal	Rarely	Mild-normal	

CHD, congenital heart defect; DEND, developmental delay, epilepsy, neonatal diabetes; DIDMOAD, diabetes insipidus, diabetes mellitus, optic atrophy and deafness; FBS, Fanconi–Bickel syndrome; HIL, hypomethylation of multiple imprinted loci; IPEX, immunodysregulation polyendocrinopathy, enteropathy, x-linked; IUGR, intra-uterine growth retardation; MODY, maturity-onset diabetes of the young; MODY, maturity-onset diabetes of the young; NDH, neonatal diabetes with congenital hypothyroidism; PNDM, permanent neonatal diabetes; RCAD, renal cysts and diabetes; SGA, small-for-gestational age; TNDM, transient neonatal diabetes; TRMA, thiamine-responsive megaloblastic anemia syndrome; WRS, Wolcott–Rallison syndrome.

suggested that other forms of neonatal diabetes were characterized by more extreme deficiency of insulin *in utero*, including six patients with homozygous GCK mutations [birth weight SDS −2.75 (−3.63 to −1.3)], 29 6q24-related NDM babies [−2.94 (−4.42 to −0.38)], as well as a small group of rare recessive causes who were the most significantly SGA (1 PDX1, 1 HNF1B, 3 PTF1A, SDS −5 to −2.5).

KATP-RELATED NEONATAL DIABETES

The most common cause of neonatal diabetes is activating heterozygous mutations in the *KCNJ11* or *ABCC8* genes that encode the two KATP channel subunits [3]. The KATP channel is a hetero-octameric structure composed of four SUR1 subunits (type 1 regulatory sulfonylurea receptor, encoded by ABCC8) surrounding four Kir6.2 subunits (inwardly rectifying potassium channel, encoded by KCNJ11) that form a central pore. Glucose metabolism leads to generation of ATP that binds to the KATP channel and causes closure, with consequent depolarization of beta cell membrane that results in insulin secretion. These patients have the KATP channels inappropriately open even in the presence of hyperglycemia preventing the depolarization of cell membrane and secretion of insulin. Importantly, the vast majority of patients with these mutations can be treated with high-dose oral sulfonylurea monotherapy instead of insulin injections with greatly improved glycemic control but without significant hypoglycemia [20–22].

Early studies showed that these patients present with low birth weight, with 58% of patients having a birth weight at or below the 3rd percentile. Patients who did not have severe neurologic symptoms had a clear catch-up growth after birth, and their weights and heights were normally distributed on follow-up after a mean of 9.3 years [19].

Neurodevelopment in KATP neonatal diabetes

Certain forms of neonatal diabetes are clearly associated with a variety of neurodevelopmental impairments. Although this includes several of the rare syndromic forms that directly affect brain development, the most common form of NDM is also associated with a spectrum of problems that can present at different ages. Those with KATP-related NDM exhibit a range of impairments that can include learning disorders, significant cognitive dysfunction and seizures [23]. Multiple factors could be contributing to the neurodevelopmental delay but the main considerations are whether they are due primarily to the diabetes and/or disability related to the severe onset of disease as an infant, or rather may be because of direct effects of the mutations that are separate from the diabetes. It is important to note that mild cognitive dysfunction has been described in long-standing type 1 and 2 diabetes, for example, difficulties in learning and memory, mild degrees of cognitive and motor slowing, decrease in attention and executive functioning. Studies of both forms of diabetes have demonstrated neural slowing, increased cortical atrophy, microstructural abnormalities in white matter tracts, with such findings being associated with chronic hyperglycemia, recurrent hypoglycemia, diabetic ketoacidosis, hypertension, microvascular complications and macrovascular disease [24–26]. As KATP neonatal diabetes patients face similar degrees of hyperglycemia and hypoglycemia, it is possible that such fluctuations may have a greater impact on an early developing brain, especially during treatment with insulin before a molecular diagnosis allows for treatment with sulfonylureas that allow for greater control of glycemia.

In contrast, several lines of evidence strongly suggest that most of the neurodevelopmental dysfunction is because of direct effects of mutated K_{ATP} channels that are widely expressed in the brain. The exact role of K_{ATP} channels in the human central nervous system (CNS) has not been fully explained, rodent studies propose that they are important for glucose sensing and may be involved in seizure propagation [27,28]. K_{ATP} channels are expressed in multiple brain areas, including cerebellum that has function in motor coordination, language and executive function [29,30].

Firstly, a mouse model of KATP-NDM has demonstrated that a phenotype including weakness was dependent on brain expression of mutant channels [31]. More importantly, the severity of neurological phenotype in humans is highly correlated to specific mutations, many symptoms show at least a mild degree of improvement after treatment with sulfonylureas [32]. One study suggested that earlier treatment may result in improved outcome [33]; however, a very recent study with patient stem-cell derived cerebral organoids suggests early disruption in the development of cortical neuronal network and may limit approaches to improve outcome [34▪].

In addition to numerous case studies, we and others have published larger cohort studies that have documented a spectrum of neurodevelopmental dysfunction that depends greatly on specific mutation. We assessed neuropsychological and behavioral dysfunction in 23 patients with *KCNJ11* mutations with and without global developmental delay treated with sulfonylurea and 20 healthy sibling controls [35]. Results showed that patients who

have mutations not associated with global developmental delay (R201H, for example) had a mild degree of neurodevelopmental dysfunction that was would be difficult to distinguish from normal, but was significantly reduced compared with their siblings: specifically intelligent quotient (IQ), vocabulary development (WASI-II), and reading achievement (WIAT-III), as well as lower performance in all measures of academic achievement and executive functioning. A survey study of parents also revealed a greater likelihood of attention-deficit hyperactivity disorder (ADHD), school dysfunction and sleep disturbance [36]. Several other studies have documented similar findings among similar patients in other countries [37–39].

CNS features have not been reported as often among those with *ABCC8* mutations, which more often cause transient neonatal diabetes. A recent study of 24 patients with sulfonylurea-treated ABCC8-PNDM found that 62% patients were reported to have CNS features before and after transfer to sulfonylureas including developmental delay in 48%, learning difficulties in 52% and ADHD in 38%. Seven of 13 patients exhibited improvement in neurological features after starting sulfonylureas [40▪▪].

6q24-RELATED TRANSIENT NEONATAL DIABETES

The most common cause of transient neonatal diabetes is overexpression of genes at chromosome 6q24, resulting from three known mechanisms: paternal uniparental disomy of chromosome 6, paternally inherited duplication of 6q24 and maternal methylation defects [41]. Although these patients experience transient diabetes, they tend to be among the most severely affected *in utero*. A large cohort study showed that most patients are born small for gestational age, with a mean weight and adjusted birthweight SD of 2001 g and −2.5, respectively [42]. Likely because of concerns about fetal growth and low birth weight, they are most often diagnosed with diabetes within the first few days of life. Although patients are most often treated initially with insulin, some patients respond to sulfonylurea during the neonatal phase [43,44]. One cohort study showed that all children with IUGR experienced catch-up growth, with height and weight being normal at 2 years of age [45]. After remitting in infancy, diabetes recurs in most patients later in life. One study of four participants showed that diabetes after recurrence was responsive to sulfonylurea with or without other noninsulin therapies with good glycemic control at reevaluation at least 5 months later [46]. Although these patients all had a neonatal history of SGA/IUGR, their adult heights and BMIs (21.7 and 31.4 kg/m^2) were not low, consistent with early recovery of most of the beta-cell dysfunction. A relatively small fraction of patients with 6q24-TNDM may have other associated clinical characteristics, such as congenital heart disease, deafness, neurologic features including epilepsy and renal malformations, though these seem more likely when defects in maternal methylation affect multiple imprinted loci beyond just 6q24 [42].

INSULIN GENE-RELATED NEONATAL DIABETES

Heterozygous mutations in the *INS* cause protein misfolding leading to retention and accumulation in endoplasmic reticulum (ER) and/or other subcellular compartments, resulting in ER stress and eventual beta-cell apoptosis [47]. In one large study, *INS* was sequenced in 1044 patients with diabetes diagnosed before 2 years of age, MODY, or young-onset type 2 diabetes and found that 12% of patients with PNDM had *INS* mutations [48]. Patients had mildly reduced birth weights, consistent with in-utero growth retardation because of reduced insulin secretion. The median birth weight was 2.7 kg (range 1.7–3.9), corresponding to the sixth percentile (range <1st to 87th). Neurodevelopmental delay has not been described in patients with INS mutation but some patients exhibit other neuropsychiatric problems that are common in all forms of diabetes, such as depression and anxiety.

CAUSES INVOLVING PANCREATIC HYPOPLASIA OR AGENESIS

Rarely PNDM is because of pancreatic hypoplasia or agenesis. Failure-to-thrive and ongoing growth concerns are common in these patients whose diabetes is further complicated by pancreatic exocrine insufficiency with or without other features.

GATA6

Heterozygous inactivating mutations in *GATA6* are the most common cause of pancreatic agenesis/hypoplasia [49]. In an early cohort of 24 patients with *GATA6* mutations, the median age at diagnosis of diabetes was 2 days and median birth weight was 1588 g (less than first percentile). Pancreatic imaging was consistent with agenesis or marked hypoplasia of the pancreas and patient studies demonstrated severe exocrine pancreatic insufficiency [50]. Extrapancreatic features are also present, with congenital heart defects being very

common and often requiring surgical correction. Additional features include congenital hypothyroidism, hepatobiliary malformations (gallbladder agenesis and biliary atresia) and gut abnormalities (intestinal malrotation and hernias). Insulin therapy, as well as pancreatic enzyme replacement therapy, is necessary for appropriate growth and glycemic control. Patients may exhibit some degree of neurocognitive dysfunction that may be at least partly related to their multiple long-term comorbidities that often require long-term hospitalization.

GATA4

In one study of five patients with neonatal diabetes because of *GATA4* mutations, endocrine phenotype was variable: two patients had neonatal diabetes, which remitted temporarily but relapsed later, while two patients had permanent diabetes, and the fifth patient was born prematurely, diagnosed with diabetes on the first day of life and died of multiple organ failure at 4 days of age [51]. The four patients with neonatal diabetes had low birth weight (less than third centile) consistent with insulin deficiency *in utero*. All patients were treated with insulin. The pancreatic exocrine phenotype was also variable. One patient had exocrine pancreatic insufficiency and received exocrine supplementation. Also congenital heart malformations were present and ranged from septal defects associated with pulmonary stenosis to atrioventricular canal defect. Developmental delay and neurocognitive defects were reported in all patients.

PDX1

Bi-allelic *PDX1* mutations are a very rare cause of pancreatic agenesis leading to early diagnosis of PNDM characterized by severe SGA [52]. Most patients will be found to have severe pancreatic exocrine insufficiency in addition to insulin-requiring diabetes but other features are not usually present. Some cases with hypomorphic compound heterozygous mutations were not found to have significant pancreatic agenesis or exocrine pancreatic insufficiency.

PTF1A

Homozygous truncating mutations in *PTF1A* cause pancreatic agenesis and neonatal diabetes, often with cerebellar agenesis [53]. Similar to patients with coding mutations, patients with enhancer mutations exhibited markedly reduced fetal growth (SDS −3.42), as well as reduced longitudinal growth during limited follow-up, possibly related to all patients also having exocrine pancreas insufficiency [54]. Neurodevelopmental outcome was not well characterized in these patients but some patients had very severe neurodevelopmental problems, including global neurodevelopmental delay, central hypoventilation and total cerebellar agenesis while others had mild neurodevelopmental delay with or without microcephaly.

OTHER RARE RECESSIVE CAUSES, OFTEN HAVING SYNDROMIC FEATURES

There is now a long list of genes important for beta-cell development and/or function for which bi-allelic mutations can cause neonatal diabetes, and often involving neurodevelopmental and/or growth concerns (Table 1).

EIF2AK3/Wolcott–Rallison syndrome

EIF2AK3 encodes the PERK protein that is responsible for regulating global protein synthesis as part of the unfolded protein response in the endoplasmic reticulum [55]. Bi-allelic mutations in *EIF2AK3* are the most common recessive cause of PNDM, with many cases having been described in countries such as India and Saudi Arabia [56,57]. As part of the Wolcott–Rallison syndrome (WRS), patients frequently exhibit other characteristics including spondyloepiphyseal dysplasia, hepatic and renal dysfunction; birth weight is often normal or only mildly reduced, age of diabetes diagnosis is quite variable, and pancreatic exocrine insufficiency has been described in some cases. A large fraction of patients appear to have some degree of neurodevelopmental impairment but this has not been well characterized longitudinally [56–58]. Growth impairment is often mentioned as a feature of WRS but only in a few cases has short stature in later childhood been described [56,57,59]; further longitudinal studies will be needed to clarify the extent of growth problems and its relationship to other features, such as skeletal dysplasia and pancreatic exocrine insufficiency.

GCK

Homozygous inactivating *GCK* mutations result in complete deficiency of glucokinase, a major regulator of glucose metabolism in pancreatic beta cells, leading to permanent neonatal diabetes mellitus, where heterozygous parents have GCK-MODY [60]. These infants present with severe intrauterine growth retardation that demonstrates the key role of *GCK* for insulin secretion *in utero*. Patients are treated with insulin, sulfonylureas can be added

to increase basal and stimulated insulin secretion. Although longer term follow-up is lacking, no significant neurodevelopmental difficulties have yet been reported.

NEUROD1

Biallelic mutations in *NEUROD1* are a rare cause of permanent neonatal diabetes that also includes cerebellar hypoplasia, sensorineural deafness, visual impairment and learning difficulties [61]. Patients were diagnosed with diabetes within the first 2 months of life but had concerns for intrauterine growth retardation (birth weights 1490 and 2230 g at 34 and 38 weeks of gestation, respectively), reflecting severely reduced insulin secretion *in utero*. Several other rare recessive causes are frequently characterized by low birth weights and a variety of syndromic features that sometimes includes direct effects on brain development (Table 1).

MONOGENIC CAUSES OF AUTOIMMUNE DIABETES

A growing list of genes important for immune function have been described as causes of autoimmune diabetes in infancy along with other immune dysfunction. Several other rare causes not discussed here have limited information on growth and development.

Immunodysregulation, Polyendocrinopathy, Enteropathy X-linked (IPEX) syndrome is caused by mutations in the *FOXP3* gene, which is important in regulatory T-cell function. The clinical course can be highly variable but diabetes is often the first feature, along with other endocrinopathies, enteropathy and exfoliative dermatitis. In addition to insulin deficiency, they will often have intractable diarrhea with villous atrophy leading to failure to thrive. One cohort described diabetes as the initial feature, with onset varying from 3 days to 3 months of life [62]. Birth weight appeared to correlate with disease severity as it was markedly reduced only in the two patients who died early in infancy. Gastrointestinal manifestations varied in severity from mild diarrhea to severe enteropathy. Patients with full IPEX can have very severe neonatal course requiring stem cell transplant; however, other patients will exhibit a more mild course where diabetes is the main feature [63].

STAT3 activation leads to impairment of the development of regulatory T cells, where heterozygous STAT3 mutations can cause neonatal diabetes along with other autoimmune dysfunction. All five patients in one cohort had IUGR, thought to be because of insulin deficiency secondary to intrauterine autoimmune destruction of beta cells [64]. Later in infancy, some patients developed autoimmune enteropathy, autoimmune interstitial lung disease, juvenile-onset arthritis and primary hypothyroidism. All patients exhibited short stature later in life (likely related to multiple clinical comorbidities) but did not exhibit significant neurodevelopmental dysfunction.

Biallelic *LRBA* mutations cause common variable immunodeficiency-8 and had been described in some patients presenting with neonatal diabetes. In one cohort of 10 patients with diabetes within the first 15 months of life, birth weight was variable and not all the patients had concerns for IUGR during pregnancy [65]. Other autoimmune disorders were present and included hematological manifestations, autoimmune enteropathy and hypothyroidism. Patients with these mutations often have very severe complications during infancy and the mortality rate is elevated. Neurodevelopmental growth was not well described but one of the patients was reported to have right hemiparesis and neuromotor retardation later in infancy.

CONCLUSION

Neonatal diabetes results from mutations in almost 30 different genes that play key roles in beta-cell and/or pancreatic development, as well as often involving other organs, such as brain. The monogenic disorders serve as models of rare human genetic disease that provide the opportunity for better understanding of molecular pathophysiology. Although many genotype–phenotype associations have been described, longer term outcome studies will be needed to further elucidation many remaining uncertainties, such as effects on adult height.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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