Incomplete Neonatal diabetes mellitus with congenital hypothyroidism (NDH) Syndrome In Saudi Patients with Known Mutations And Different Manifestations: a case report and brief literature review

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Abstract

Permanent neonatal diabetes may occur either in isolation or associated with multi-organ syndromes. It is caused by mutations in the genes responsible for pancreatic β cell mass or function. We report new cases of consanguineous parents from

Saudi Arabia with a homozygous deletion of exons 1and 2, and exon 5-9 of the GLIS3 gene, who presented with permanent neonatal diabetes associated with intrauterine growth retardation, severe congenital hypothyroidism without other manifestation in the liver, renal or eyes in the 1st one and cystic renal changes in the 2nd patient. Mutations in the GLI-similar 3 (GLIS3) gene encoding the transcription factor GLIS3 are a rare cause of neonatal diabetes and congenital hypothyroidism with only 15 reported patients worldwide to date.

Keyword: Neonatal diabetes, Congenital hypothyroidism, GLIS3

Introduction

Mutation in the human GLI-similar 3 (GLIS3) gene (NM_001042413) are reported in the literature to be one of the rare cause of neonatal diabetes and congenital hypothyroidism (CH). the 11 exon GLIS3 gene express early in embryogenesis and it has a critical role in the cellular regulation and development by functioning as a suppressor or activator of transcription factor, this transcription factor found recently that it is containing five Krüppel-like zinc finger motifs.

The first patients presented with this autosomal recessive mutation in GLIS3 had a classical features of this syndrome including the intrauterine growth retardation, dysmorphic features, neonatal diabetes and hypothyroidism, later on developed a progressive hepatic fibrosis, renal cystic dysplasia and congenital glaucoma and he died at early infancy secondary to infection.

Despite the rarity of this condition, we found in our community tow patients who carry the mutations of this interesting syndrome. Both patients of consanguineous parents from Saudi Arabia with a homozygous deletion of exons 1and 2 in the first one, and exon 5-9 of the GLIS3 gene in the second patient, who presented with permanent neonatal diabetes associated with intrauterine growth retardation, severe congenital hypothyroidism without other manifestation in the liver, renal or eyes in the 1st one and cystic renal changes in the 2nd patient. Mutations in the GLI-similar 3 (GLIS3) gene encoding the transcription factor GLIS3 are a rare cause of neonatal diabetes and congenital hypothyroidism with only 15 reported patients worldwide to date.

Case presentation

Patient I

Our patient is 3 years old girl, referred to us at age of 29 days, as a case of intrauterine growth retardation (IUGR), full-term female to consanguineous Saudi parent (1st-degree cousins). She was born with a weight of 1.74 kg, length of 46 cm, Abgar score 6 & 9 at 1st, and 5th minute respectively. Her physical examination was normal with no dysmorphic features.

Her cord Thyroid Stimulating hormone (TSH) level was extremely High (526.37IU/L). Repeated serum TSH was 598.28IU/L (normal 0.27–4.2) and free thyroxine (FT4) of < 5.15pmol/L (normal 12–22).

She was managed by oral Thyroxine 25 mcg daily. Repeated thyroid function after starting treatment was normal (TSH4.87IU/L, T4 17.94 IU/L) and further investigation for thyroid anatomy which was assessed by thyroid scan was normal.

She developed hyperglycemia in the first few hours of life, glucose level was reaching 20-26mmol/l persistently, initially was treated with insulin infusion as a case of hyperglycemia secondary to stress and IUGR, showed no improvement, then referred to us. We start her on diluted short-acting insulin but we discontinue it because of severe

hypo and hyperglycemia. The patient shifted to subcutaneous long-acting insulin but again the target blood glucose has been difficult to achieve due to labile glucose level (mainly hyperglycemia with no ketoacidosis and few episodes of asymptomatic hypoglycemia). A trail of an insulin pump for 2 days was failed as she has persistent hyperglycemia despite changing the dose of basal and bolus insulin. So subcutaneous long-acting insulin was resumed with frequent glucose level monitoring every 2-4hours. When we reach the acceptable target, she was discharged on the same type of insulin. currently, she is on long-acting insulin 8 units daily with short-acting insulin as needed and her blood glucose level between 6.6-8.8mmol/L.
As the patient is having Diabetes mellitus and Congenital hypothyroidism, GLS3 mutation for NDH Syndrome was suspected and further investigation was done to look for more features. She was maintaining normal liver function tests, electrolytes Adrenocorticotropic hormone (ACTH), and cortisol level. Abdominal and renal ultrasound & Brain MRI were normal. A skeletal survey showed no skeletal abnormalities. She has a normal hearing test and Ophthalmic examination.
Consent was obtained from her parent to perform genetic analysis. The coding axons 2-11 as well as the corresponding exon-intron boundaries of the GLIS3 gene on chromosome 9p24.2 (OMIM 610192) were enriched using Roche/NimbleGen sequence capture technology and sequenced on an Illumina HiSeq 1500s.result was the Detection of homozygous deletion of exons 1and 2 of the GLIS3 gene.

Patient II

15 months old Saudi boy, product of consanguineous marriage and uncomplicated pregnancy, originally from Hafar Albatin born with a birth weight of 1.5 kg. He had almost 40 days of stay in the neonatal ICU at periphery hospital where he was diagnosed as IUGR, congenital hypothyroidism, and hypoglycemia followed by hyperglycemia that was managed as stress hyperglycemia. Few days after discharge, the patient admitted to our hospital as a case of neonatal diabetes-related hyperglycemia, IUGR, failure to thrive, congenital hypothyroidism on suboptimal dose and persistence high TSH up to 400 (normal 0.7- 6.4), and cholestasis with high Aspartate transaminase (AST) 263 U/L (normal15-37), Alanine transaminase (ALT) 97U/L (normal 12-78), Gamma-glutamyltransferase (GTT) 243 U/L (normal 5-85), direct bilirubin 45 umol/L (normal 0 - 3.4) and total bilirubin 61 umol/L (normal 3.40-17) that could be related to the sub-optimal treatment of hypothyroidism or part of an undiagnosed syndrome. NDH syndrome was suspected and a genetic test was sent immediately taking into consideration the presence of a brother who was diagnosed to have congenital glaucoma. Other investigation reveals normal retinal examination, normal initial renal, and liver ultrasound. Diabetes management was challenging because of small weight and high sensitivity to insulin, several regimens were tried including Once per day long-acting insulin, and as per needed doses of rapid-acting insulin without basal insulin but all trials end with severe hypoglycemia that required multiple admission through his first few months of diagnosis. The insulin pump was unavailable. For that, his glucose level was fluctuating with an average A1c of 9. However, the patient starts to show good response at age of one year to multiple doses of insulin (MDI) in form of long-acting insulin and rapid-acting insulin. Subsequent investigation of thyroid and thyroxin doses adjustment attains stable FT4 but not for TSH which was wiggling between 18.7-9.57 pmol/l while liver panel improved dramatically to be (AST 46.6 U/L normal15-37, ALT 27.8 U/L normal 12-78, direct bilirubin 2.6 umol/L normal 0 - 3.4, total bilirubin 8.3umol/L normal 3.40-17). By that time the genetic test confirms the diagnosis of NDH syndrome

by the presence of homozygous deletion on chromosome 9p affecting exons 5- 8 of the GLS3 gene. For that, a multidisciplinary team involved in the case including a pediatric Endocrinologist, Pediatric Gastroenterologist, Pediatric Genetics, Pediatric Nephrologist, Diabetic educator, Ophthalmologist, and social worker. Lately, renal ultrasound at age of 15 months documents a mildly enlarge kidney with increase parenchymal echogenicity and diffuse tiny cystic changes that suggest Polycystic kidney disease with preserve normal renal function test.

Discussion:

Neonatal diabetes mellitus with congenital hypothyroidism (NDH) syndrome is a rare syndrome caused by homozygous or compound heterozygous mutations in the GLIS3 gene (OMIM#610192) on chromosome 9p24 and encodes a full-length protein of 90 kD in size. It was expressed in a dynamic pattern during eye and other organs development, also consider as a master regulator of several pathways and involved in several endocrine glands' development and function.[1]
This syndrome is characterized by IUGR, severe resistant congenital hypothyroidism, and the onset of nonimmune diabetes mellitus within the first few weeks of life. Other features include skeletal involvement, congenital glaucoma, renal parenchymal disease, renal cystic dysplasia, a hepatic disease with hepatitis in some patients and hepatic fibrosis, and cirrhosis in others, sensorineural deafness, and learning difficulties.[1][2][3][4][5] Facial dysmorphism, when present, consistently involves low-set ears, epicanthal folds, upslanted palpebral fissures, a flat depressed nasal bridge with overhanging columella, long philtrum, and thin upper lip.[2][6] These data strongly suggest that genetic variations and mutations in GLIS3 have strong cross phenotypic effects in distinct organs.[7]

Glis3 is expressed during pancreatic development although despite its key role in diabetes and in endocrine pancreatic development; molecular and cellular mechanisms mediating its function remain largely unknown.
Recent human genetic studies implicated GLIS3 in a syndrome with NDH and suggested a regulatory function for GLIS3 in the pancreas. GLIS3 expression confoundingly also promotes beta-cell proliferation and regulates insulin gene expression through binding to GLI-RE on the INS gene during the embryonic period. Therefore, the variation in insulin sensitivity between patients with GLIS3 mutations may relate to the impact of the mutation on the nuclear localization, GLI-binding element activity, transactivation, pancreatic development, subsequent cell proliferation, and remnant endogenous insulin production. In humans, GLIS3 has been identified as a susceptibility locus for the risk of type 1 and 2 diabetes.[7][8][9][10]

Defects in the GLIS3 gene are reported to be a rare cause of congenital hypothyroidism (CH) and neonatal diabetes. Chunyun Fu et al conduct a study to examine the prevalence of GLIS3 mutation among CH patients. So, he collected blood samples from 592 patients with CH, and genomic DNA for all exons of the GLIS3 gene was extracted. He found that only 2 patients out of 592 CH patients revealed heterozygous deletion GLIS3 variant combined with compound heterozygous DUOX2 mutations and he conclude by the prevalence of GLIS3 variations which was only 0.3% among studied Chinese CH patients.[4]
The absence of consistent pathological features makes it difficult to determine a causative mechanism of hypothyroidism in GLIS3 gene mutation. In most cases, patients

have not responded to medical treatment and they presented with elevated levels of TSH despite normalization of T4. However, abnormalities in thyroid anatomy and/or thyroid uptake scan are not sufficient to explain this.[11]

Hashimoto et al found that the GLIS3 gene is identified as the causal gene of Polycystic Kidney Disease (PKD).[9] It is expressed in the epithelial cells of the pancreas and renal tubules and ducts.
Further reports also demonstrated that patients with GLIS3 mutations presented with a wider phenotypic spectrum than initially reported. Skeletal manifestations were first described in 2011[12] in a patient with a GLIS3 mutation (deletion in exons 1 to 2) presenting with multiple rib fractures with persistence of callus formation and scoliosis. Those patients have a defect in bone remodeling suggested by the persistence of callus formation either due to osteoblast signaling to osteoclasts dysfunction or reduction of osteoclastic bone resorption.[5]

Although the GLIS3 gene is expressed during embryogenesis of brain tissue, the data connecting between GLIS3 with brain development are insufficient, also it is found a relation between GLIS3 mutation and Learning difficulties and risk of Alzheimer's disease but the role of this process are not understood.[5]
In 2006, Vale´rie Sene´e et al studded 6 patients with NDH syndrome, tow out of 6 have mild mental retardation and 3 patients died at age of 10 days, 6 months, and 16 months. The three individuals died from pneumonia and respiratory failure or sepsis.[13]

GLIS3 is expressed in multiple body tissue, with the highest levels in the pancreas, kidney, thyroid gland, thymus, testis, and uterus, and lower levels were described to be express in the brain, lung, ovary, and liver.[1]

The larger transcript of GLIS3 (7.5 kb) is predominantly expressed in the pancreas, thyroid, and kidney, while the smaller isoforms (0.8–2 kb) are mainly localized in the heart, kidney, liver, and skeletal muscle. But despite the different patterns of expression, there is no evidence of variable pathophysiological functions so far or in these different transcripts.[1]

The Gli-similar family of Kruppel-like zinc finger proteins is comprised of three proteins, Glis1-3. Glis1 was first identified by a yeast two-hybrid screening using the ligand-binding domain of the retinoic acid-related orphan receptor γ (RORγ) as bait.[3]
Subsequently, two additional members of the family were identified that possessed high levels of homology with the zinc fingers of Glis1 and were termed Glis2 and Glis3.[12][14]
GLI-similar 3 (GLIS3) is an identified transcription factor containing five Kruppel-like zinc finger motifs.[15] GLIS3 expression occurs early in embryogenesis and is thought to play a critical role in the cellular regulation of development by functioning as a repressor or activator of transcription.[15][16] The human GLIS3 gene is located on chromosome 9p24.2 and encodes a protein that is approximately 90 kD in size.[11]
Mutations in GLIS3 (9p24.2, OMIM#610192) have been described in the literature as a rare cause of neonatal diabetes.

In 2003, Taha and colleagues described two siblings for a consanguineous Saudi Arabian family who had intrauterine growth retardation, neonatal diabetes and hypothyroidism,

progressive hepatic fibrosis, renal cystic dysplasia, facial dysmorphism, and congenital glaucoma.[17] In 2006, Senee et al performed Genome-wide linkage analysis and sequencing of candidate genes on this family and they identified a homozygous frameshift mutation (c.1873dupC) in the GLIS3 gene which is likely to result in transcript degradation by nonsense-mediated decay, these patients died from an infection in infancy.[13] Later on, 2015, Dimitri et al described the genetic and clinical features of those 12 patients who had GLIS3 mutation, have presented with a wider phenotype consisting mainly of neonatal diabetes and congenital hypothyroidism, in addition to multiple features involving different organs.[2] In two other families with an incomplete syndrome, the affected individuals found to be harbor deletions affecting the 11 or 12 5'-most exons of the gene. The absence of a major transcript in the pancreas and thyroid (deletions from both families) and an eye-specific transcript (deletion from one family), together with the residual expression of some GLIS3 transcripts, seems to explain the incomplete clinical manifestations in these individuals.[13]

In 2017 Alghamdi et al reported a new case who presented with neonatal diabetes mellitus, severe resistant congenital hypothyroidism, cholestatic liver disease, bilateral congenital glaucoma, and facial dysmorphism. There were associated abnormalities in the external genitalia in form of bifid scrotum, bilateral undescended testicles, microphallus, and scrotal hypospadias that have not been previously described.[8]
The variation in the GLIS3 phenotype is attributed to the tissue expression of variable length transcripts derived from the 11 exon GLIS3 gene.[18]

The GLIS3 gene is expressed in multiple tissues during embryogenesis, this provides a rationale for the presentation of multisystem disease.[2] This feature is not required to be found in all patients who have the mutation.
By summarizing previously reported cases in Tables 1 & 2, Apart from patient number 1, all patients were diagnosed with congenital hypothyroidism. Developmental delay and intrauterine growth retardation (IUGR) are confined to be a common feature. Twelves out of fifteen patients presented with dysmorphic features, consistent with low-set ears, epicanthic folds, a flat nasal bridge, and a long philtrum with a thin upper lip.[2]
Liver disease was documented in 10 out of 15 patients. The hepatic dysfunction presented concomitantly with renal abnormalities and ranged from hepatitis (patients 3b and 4) to hepatic fibrosis and cirrhosis (patients 2, 3a, 6,7, 9, and 10). 11 patients have anatomical kidney changes, variable renal cystic dysplasia ranging from an isolated cyst to extensive cystic renal dysplasia. Skeletal manifestations were described recently in 2011. When we collect all patients with GLIS3 mutation we found that only Four patients had skeletal manifestations presented either as milder skeletal manifestations such as osteopenia and craniosynostosis, to significantly delayed rib fracture healing with the persistence of callus formation. And marked thoracolumbar scoliosis was found in those patients as well.
Malabsorption due to exocrine pancreatic insufficiency as demonstrated by low fecal elastase was a feature in patients 2, 3a, 3b, and 7. The congenital cardiac disease was described in Patient Number 11 who had an ostium secundum defect. It is likely that the patent ductus arteriosus observed in patients 3a and 10 was due to prematurity rather than to an abnormality in GLIS3 function. Patient 12 is the only case reported with abnormalities in the external genitalia in form of bifid scrotum, bilateral undescended testicles, microphallus, and scrotal hypospadias.[8]

Additional rare features in patients with GLIS3 mutations included pancreatic and splenic cystic change, sensorineural deafness, hiatus hernia, and choanal atresia.[2] Although, there are evidence points to the possibility of the defective GLIS3 results in a reduction in gonocytes, and spermatogonial progenitors when they found points to a novel role of GLIS3 in postnatal spermatogenesis, however, all published patient with GLIS3 mutations still in childhood period and not reach puberty yet, so the impact of this mutation on human fertility remains unknown.[2]
Also, GLIS3 mutation is expressed in malignant ependymomas and renal carcinomas.[3]
In comparison between our patients and other patients with the same mutation, you will find that our first patient with a mutation in exons 1&2 has only neonatal diabetes and congenital hypothyroidism, in contrast to other patients with the same mutations who have a skeletal disease, developmental delay, facial dysmorphism, liver disease, renal disease, exocrine pancreatic disease, congenital glaucoma, dysmorphic facial features, and CHD inform of Ostium Secundum Atrial septal defect (ASD). While our 2nd patient with a mutation in exons 5-9 has neonatal diabetes, congenital hypothyroidism, and started to has polycystic kidney disease, while the other has also liver disease, developmental delay, and facial dysmorphism.

Table 1 & 2

Patient No.	Exon	Birth Weight(g)	IUGR	GA	Ethnicity	Sex	consanguineous	age of onset of PND	congenital hypothyroidism	Liver Disease	Renal disease
1	5	2750	No	39	Caucasian	F	No	30 hr	No	No	No
2	1-2	1170	Yes	35	Bangladeshi	F	Yes	3 d	Yes	Yes	Yes
3a	1-4	1430	Yes	35	Caucasian	F	No	4 d	Yes	Yes	Yes
3b	1-4	2020	Yes	38	Caucasian	F	No	2 d	Yes	Yes	Yes
4	5-9	1750	Yes	34	Arab	F	Yes	2 d	Yes	Yes	Yes
5	4	2050	Yes	39	Arab	F	Yes	5 d	Yes	No	No
6	9-11	1530	Yes	37	African-American	F	Unknown	7 d	Yes	Yes	Yes
7	10-11	1235	Yes	36	Yemeni	F	Yes	3 d	Yes	Yes	Yes
8	4-	1860	Yes	39	Pakistani	F	Yes	24 h	Yes	No	Yes
9	3-4	1520	No	30	Turkish	F	Yes	21 d	Yes	Yes	Yes
10	4	973	Yes	31	Kurdish	F	Yes	31 d	Yes	Yes	Yes
11	1-2	1730	Yes	39	Arab	F	Yes	19 d	Yes	No	Yes
12	9	1300	Yes	36	Saudi	M	Yes	2 d	Yes	Yes	No
13a	--	2200	Yes	39	Saudi	F	Yes	2 d	Yes	Yes	Yes
13b	--	1500	Yes	37	Saudi	M	Yes	-	Yes	Yes	Yes

Patient No.	Exocrine Pancreatic Disease	Congenital Glaucoma	Skeletal Disease	Developmental Delay	Facial Dysmorphism	Other Feature	Mutation
1	No	No	No	Yes	No	Choanal atresia, hiatus hernia	p.Arg589Trp/exons 1–11 del
2	Yes	No	Yes	Yes	Yes	No	Exons 1–2 del/exons 1–2 del
3a	Yes	No	No	Yes	Yes	Bilateral sensorineural deafness, PDA, Pancreatic Cyst	Exons 1–4 del/exons 1–4 del
3b	Yes	No	No	Yes	Yes	Pancreatic Cyst, Splenic Cyst, Bilateral sensorineural deafness	Exons 1–4 del/exons 1–4 del
4	No	No	No	Yes	Yes	Yes	Exons 5–9 del/exons 5–9 del
5	No	No	Yes	Yes	No	No	p.Cys536Trp/Cys536Trp
6	No	Yes	Yes	Yes	Yes	No	Exons 9–11 del/exons 9–11 del
7	Yes	Yes	No	Yes	Yes	No	Exons 10–11 del/exons 10–11 del
8	No	No	Yes	No	No	Right sensorineural deafness	p.Gly311Alafs/p.Gly311Alafs
9	No	No	No	Yes	Yes	No	Exons 3–4 del/exons 3–4 del
10	No	Yes	No	No	Yes	Patent Ductus arteriosus	p.His561Tyr/p.His561Tyr
11	No	Yes	No	No	Yes	Ostium secundum ASD	Exons 1–2 del/exons 1–2 del
12	Yes	Yes	No	Yes	Yes	Genital abnormalities	p.Pro772leufs*35/ p.Pro772leufs*35
13a	Yes	Yes	No	--	Yes	No	Unknown
13b	Yes	Yes	No	--	Yes	No	Unknown

Conclusion:

Mutations in the GLI-similar 3 (GLIS3) genes are a rare cause of neonatal diabetes and congenital hypothyroidism with only 15 reported patients to date. We should be highly suspicious of this syndrome when we treat a neonate with congenital hypothyroidism and persistent hyperglycemia and suspected neonatal diabetes. Also we have to keep in our mind that the lack of other manifestations doesn't rule out the possibility of this syndrome.

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