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Case Report

Clinical and Genetic Characteristics and Outcome in Patients with Neonatal Diabetes Mellitus from a Low Middle-Income Country

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What is already known on this topic?
Neonatal diabetes mellitus is a rare disorder where a genetic defect is identified in 80% of cases. The confirmation of these genetic defects plays a major role in further management and follow up of these patients.

What this study adds?
This study shows a genetic diagnosis in 96% of the cases of neonatal diabetes mellitus.

Abstract
Neonatal Diabetes Mellitus (NDM) is a disorder characterized by persistent, severe hyperglycemia presenting during the first 6 months of life. These disorders are rare and the incidence is approximately 1 in 90,000 live births. To describe the clinical presentation, molecular genetics and outcome of patients with NDM from a single paediatric endocrine center from a low middle income country. A retrospective study was conducted on patients diagnosed with NDM. Medical records were reviewed for demographic data and data on clinical, biochemical and genetic analysis. 96% of patients who underwent mutation analysis had pathogenic genetic mutations on Sanger sequencing. Permanent NDM (PNDM) was diagnosed in 19 patients with 3 of them having a syndromic diagnosis. The commonest mutation was found in KCNJ11 gene. Majority of the PNDM (63%) presented with severe diabetic ketoacidosis. All patients with Transient NDM (TNDM) remitted by 6 months of age. 47% of the cases with PNDM made a switch to sulfonylurea therapy with good glycemic control (glycosylated Haemoglobin A1C 6-7.5). Data from the Sri Lankan cohort is comparable with other populations. The majority of cases are due to KCNJ11 mutations resulting in PNDM.
Keywords: Neonatal diabetes, genetics, clinical features, management, follow up

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Introduction
Neonatal Diabetes Mellitus (NDM) is a disorder characterized by persistent, severe hyperglycemia presenting during the first 6 months of life[1,2,3]. It can infrequently present between the ages of 6 months to 1 year[1,2,4]. It is a rare occurrence with a reported incidence of 1 in 90,000 live births[1,2,4]. According to the phenotypic characteristic of insulin requirement the cases of neonatal diabetes mellitus can be categorized as transient neonatal diabetes mellitus(TNDM) and permanent neonatal diabetes mellitus(PNDM)[3,5]. In up to 80% of the cases, a genetic mutation has been recorded[2,3]. These mutations cause neonatal diabetes mellitus by 3 major pathophysiological processes: malformed pancreas with abnormal beta cells, functional alteration of insulin secreting cells causing abnormal insulin synthesis and destruction of beta cells[1,2].
Anomalies of the 6q24 locus and mutations of the *ABCC8* and *KCNJ11* genes are frequent genetic causes of abnormal beta cell function[1]. These defects and the *UDP 6* mutation often cause TNDM[3,6]. Mutations in *ABCC8* and *KCNJ11* are common in families without consanguinity[7]. These mutations are also responsible for causing Maturity Onset Diabetes of the Young (MODY)[7].
Genetic causes of PNDM remain obscure in most cases. In the non-consanguineous PNDM population, mutations in the ATP sensitive potassium channel and mutations in the *INS* gene are the most common finding, whereas in consanguineous families' mutations in the *INS*, *GCK* and *EIF2AK3* genes account for the majority of cases[3].
Studies on clinical and genetic characteristics of patients with NDM in South Asia are scarce. The diagnosis and genetic confirmation of these patients opens avenue to a spectrum of management and follow up options[8].
In this study we aim to describe the clinical presentation, molecular genetics and long term follow up of a cohort of 24 patients with NDM from a single paediatric endocrine center in Sri Lanka.

Patients and Methods
Study design and participants
Patients
An observational study of 24 registered cases of Neonatal Diabetes Mellitus presenting before 1 year of age were included in the study.
Methods
Information collected from patients' records included demographic data (gender, age), clinical presentation, anthropometric measurements, laboratory findings at diagnosis, details on genetic analysis, treatment methods, co morbidities and adequacy of glycemic control on follow up. At diagnosis, the onset of diabetes mellitus and its complications were based on assessment of blood glucose levels, blood gases and electrolytes. Assessment of glycemic control was based on three monthly glycosylated Haemoglobin A1C (HbA1C) levels. The values of HbA1c were categorized as good control (6 - 7.5%), fair control (7.51 - 9%), and poor control (> 9%) Anthropometric measurements were taken by medical officers. Weight, height and body mass index were expressed as standard deviation scores according to the Centre for Disease Control and prevention 2000 growth charts.
Genetic analysis

Written, informed consent was taken from parents of patients who underwent genetic testing. Peripheral blood samples for genetic analysis were sent to University of Exeter Medical School, Exeter, United Kingdom. Genetic testing was undertaken for *ABCC8, KCNJ11, INS* and other mutations known to cause NDM. Analysis of the coding regions and exon/intron boundaries were done by targeted next generation sequencing. Sanger sequencing analysis and targeted next generation sequencing was used to confirm the genetic mutation in appropriate cases.

Results

Patient no. 19 with Trisomy 21 was found to have a recently recognised subtype of neonatal diabetes that is autoimmune but not Human Leukocyte Antigen (HLA) associated. All other genetic causes were ruled out by sequencing and the NDM was found to be aetiologically caused by trisomy 21. Unfortunately, this patient was lost to follow up after 8 months of age with the onset of the Covid pandemic. With this regard, this patient was not accounted for in the study sample.

Genetic analysis

Of the 24 patients with neonatal diabetes mellitus, 19(79%) were diagnosed with PNDM and 5(21%) had TNDM. Of the 5 patients with TNDM, 3 showed a 6q24 mutation. The remaining TNDM patients showed a mutations of the *ABCC8* and *INS* genes. The genetic mutations responsible for the cases of PNDM are illustrated below.

19 mothers of the 24 NDM patients also underwent genetic testing, out of which 11 were unaffected, 7 were heterozygous for various mutations and were deemed to be carriers and 1 mother was affected. The affected mother was diagnosed at 2 months of age. Currently, she is 30 years old, on insulin, with a fairly controlled diabetes.

20 fathers of the 24 NDM patients underwent genetic analysis. 12 fathers were unaffected. 5 were heterozygous and 2 showed non paternity. The affected father is currently on sulfonylurea therapy with well controlled diabetes.

Clinical presentation

12 of the 24 patients (50%) were female and 12 (50%) were male.

Presented in figure 2 are the age at presentation of the NDM study cohort. A point of interest is that 4 out of the 5 patients with TNDM presented before 4 weeks of age.

Patient no. 09 presented at 40 weeks and patient no. 21 presented at 28 weeks and Both of these patients who presented after 6 months of age were positive for the *ABCC8* mutation.

Of the 19 patients with PNDM, 12 (63%) presented with severe DKA. 5 patients amongst the 12 who presented with severe DKA were complicated with severe hypernatremia (serum sodium >170 mmol/l) and 4 patients suffered from stroke.

Complications and comorbidities

Patient no. 7 who presented with severe DKA and severe hypernatremia underwent amputation of the toes of the right lower limb due to thrombosis of the peripheral vessels. The initial peripheral cyanosis extended above the ankle. However, with low molecular weight heparin infusion the dry gangrene was only localized to the toes which required amputation.

Patient no. 13 with the *EIF2AK3* mutation causing Wolkott Rallison Syndrome has had three episodes of liver failure, genu valgum, scoliosis and atlanto occipital subluxation requiring fixation. Despite these efforts he succumbed to severe pneumonia at 8 years of age.

Patient no. 14 with Wolkott Rallison Syndrome is currently being followed up at the clinic with a mean HbA1C of 8%. However, he is severely disabled with kyphoscoliosis and is wheel chair bound.

Patient no. 15 with Immune mediated Polyendocrinopathy and Enteropathy X linked (IPEX syndrome) caused by the *FOXP3* mutation presented with nephrotic syndrome and alopecia and was found to have NDM at 11 months of age. He passed away at 2 years of age due to severe pneumonia and pleural effusion complicated with sepsis.

Follow-up

All patients with TNDM were weaned off drugs by 6 months of age with regular monitoring of HbA1C levels.

8 patients (42%) with PNDM, including patient no. 20 who's genetic etiology is unknown, are receiving insulin with fair glycemic control (mean HbA1C of 8%). The 9 patients who made a successful switch to sulfonylureas have good glycemic control with mean HbA1C of 7.3%. These patients are being regularly followed up at the clinic in view of evaluation for development of complications of diabetes and assessment of growth and development.

Of the 4 patients who suffered from a stroke at presentation, 2 patients have delay in achieving age-appropriate developmental milestones. All patients, apart from patient no. 14 with Wolkott Rallison syndrome, are showing satisfactory weight and height gain.

Discussion

In the past there have been a number of reports on clinical characteristics of NDM in European and Middle Eastern cohorts. To date there have been no published reports from Sri Lanka on comprehensive data on NDM including genetic analysis. This is mainly because data on NDM, especially in view of long term follow up and genetic analysis is scarce. We hereby present the clinical presentation, genetic analysis and ~~long term~~ glycemic control of patients with NDM in a single paediatric endocrine center in Sri Lanka.

Genetic Analysis

In comparison to the percentage of patients with PNDM in the Israeli cohort at 57%, in the American cohort at 70% and the Indian cohort at 50%, our cohort had 83% with PNDM which is higher than the percentage of patients with PNDM in the other cohorts[2,3,9]. The most common genetic etiology for PNDM was mutations in the *KCNJ11* gene (42%). This finding agrees with previous records of European and Middle eastern populations where mutations of the *ABCC8, KCNJ11* and *INS* genes were found to be the most frequent etiologies for PNDM[3,7].

Of the 19 patients with PNDM, 3 tested positive for genetic mutations consistent with syndromic forms of PNDM. 2 were positive for the *EIF2AK3* mutation and 1 was positive for the *FOXP3* mutation. Mutations in transcription factors involved in embryological development of the pancreas and elevated endoplasmic reticular stress giving rise to destruction of beta cells are two mechanisms involved in the pathogenesis of NDM in syndromic forms. In this regard, mutations in the *EIF2AK3* gene are responsible for beta cell destruction due to increased stress on the endoplasmic reticulum whereas mutations of the *FOXP3* gene is responsible for immune mediated damage to beta cells[2].

60% of the cases with TNDM tested positive for mutations in 6q24 gene which is in keeping with data from Middle Eastern (70%) and American cohorts. Mutations in the *ABCC8* and *KCNJ11* genes were the second most common causes of TNDM in the above mentioned cohorts[2,3]. However, in our cohort, the other cases of TNDM were found to be due to a mutation in the *INS* and *ABCC8* genes.

Clinical Presentation

Cases of TNDM present earlier than PNDM[1,3,10]. More specifically, patients with 6q24 mutation present earlier than those with potassium channel defects. This is evident in our cohort where 4 out of the 5 patients with TNDM presented before 4 weeks of age. 9.6 weeks was found to be the median age at presentation of cases with *KCNJ11* or *ABCC8* mutations. However, presentation after 6 months of age has also been reported[2]. Even in our cohort two patients with *ABCC8* mutation and one patient with *KCNJ11* mutation presented after 6 months of age.

Presentation with DKA was more common in patients with PNDM when compared with cases of TNDM[10]. 78.8% cases with mutations of *KCNJ11* or *ABCC8* presented with DKA whereas cases with TNDM due to overexpression of 6q24 did not present with DKA in the American cohort[2]. This is evident in our cohort where none of the cases of TNDM presented with DKA. This is because the duration of

insulinopenia is less in TNDM due to the earlier age of presentation[2] and the potassium channel mutations giving rise to PNDM cause a severe lack of insulin due to hyperpolarization of the membrane. This leads to marked reduction in insulin secretion whereas in TNDM there is only a reduction in beta cell function giving rise to a modest reduction in insulin secretion[3]

During the latter part of pregnancy insulin plays a major growth promoting role[6]. Therefore, the lack of insulin leads to the low birth weight[1,3]. All the patients in our cohort with K – ATP channel mutations had normal birthweight (birthweight >2.5 kg)

Observation of growth parameters in our cohort revealed that all patients excluding patient no. 14 with Wolkott Rallison syndrome showed satisfactory height and weight gain which can be attributed to proper glycemic control.

Complications and Co morbidities

Patients no. 1 and 2 with PNDM had a severe course complicated with DKA, hypernatremia and stroke. Fortunately, they are currently achieving age appropriate developmental milestones. They are on sulfonylureas therapy with good glycemic control (mean HbA1C 7%)[11].

Patients no. 3 and 12 also had a severe course complicated with severe DKA and stroke. However, their course was further convoluted with developmental delay and they are currently receiving multi-disciplinary care. They have a fairly controlled diabetes with a mean HbA1C of 8.5% [11].

The remaining 20 patients have no concerns regarding achievement of age-appropriate developmental milestones.

Follow up

Successful treatment with sulfonylureas has been achieved in patients with *ABCC8* and *KCNJ11* mutations[1,2,3]. The KCNJ11 and ABCC8 genes code for the Kir6.2 subunit and the SUR 1 ion-channel regulator subunit of the K- ATP channel respectively[4]. Sulphonylureas act on the K- ATP channel to induce closure of the channels thus causing release of insulin from beta cells[6]. Management with sulphonylureas have the advantages of reducing the incidence of hypoglycemia and improving the neurological and visual impairment in patients if introduced early[1,12]. The most frequently used sulphonyurea in NDM is glibenclamide[2]. 9 out of the 12 patients with *ABCC8* or *KCNJ11* mutations in our cohort are currently on Glibenclamide with a good glycemic control (mean HbA1C 7.3%)[11].

8 patients with PNDM are currently on insulin administered according to the multiple daily dose regime. Initial management while the patient is on milk feeds is with long acting insulin agents. With the introduction of complimentary food, short acting insulin prior to meals are initiated. It is a point to note that due to financial and socio-economic constraints none of our patients are on insulin pumps. Furthermore, capillary sugars are checked using auto lancets as the luxury of continuous glucose monitors are not financially feasible in Sri Lanka. Glycemic control in this cohort is fair with mean HbA1C of 8%

Study Limitation

As this study was conducted in a single center in Sri Lanka the true incidence rate of NDM across the country cannot be estimated. This is a limitation of our study.

Conclusion

Data from our cohort is comparable with other populations. PNDM accounts for majority of the cases with mutations of the *KCNJ11* responsible for a higher percentage of the cases. TNDM presents at an earlier age and remits by 6 months of age. The proportion of patients with PNDM presenting with severe DKA is more in comparison to patients with TNDM. Patients with *ABCC8* and *KCNJ11* mutation more frequently make a successful switch to sulfonylurea therapy.

A diagnosis of NDM should be considered in neonates and infants with persistent refractory hyperglycaemia. Genetic testing should be considered as knowledge regarding the specific causative genetic mutation can appreciably modify the course of treatment.

Close follow up is required in all patients with NDM in view of screening for complications and assessment of growth and development.

Authorship Contribution

Concept: N Atapattu, I.M Kumarasiri, Design: N Atapattu, I.M Kumarasiri, T.J Hoole, I Jayasundara, Data collection or processing: N Atapattu, I.M Kumarasiri, R Balasubramaniam, M.W.A Nimanthi, Analysis or interpretation: N Atapattu, I.M Kumarasiri, Literature search:N Atapattu, I.M Kumarasiri, T.J Hoole, I Jayasundara, R Balasubramaniam, M.W.A Nimanthi, Writing: N Atapattu, I.M Kumarasiri

Disclosure

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Conflicts of interest

The authors report no conflicts of interest in this work.

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Table 1. Results of genetic analysis and management of the neonatal diabetes mellitus cohort population

Patient No.	Status	Current Management	Mutation	Maternal status	Paternal status
1	PNDM	Sulfonylurea therapy	Gene - *KCNJ11* Zygosity – Heterozygous HGVS description -NM_000525.3:c.602G>A p.(Arg201His) Location: GRCh37 (hg19) Chr11:g.17409037 Classification - Pathogenic	Unaffected	Affected
2	PNDM	Sulfonylurea therapy	Gene : *KCNJ11* Location : Exon 1 DNA Description : c.149G>A Protein Description : p.Arg50Gln (p.R50Q) Consequence : Missense	Unaffected	Unaffected
3	PNDM	Insulin	Gene : *KCNJ11* Location : Exon 1 DNA Description : c.149G>C Protein Description : p.Arg50Pro (p.R50P) Consequence : Missense	Unaffected	Unaffected
4	PNDM	Sulfonylurea therapy	Gene : *KCNJ11* DNA Description : c.2972G>A Protein Description : p.Ser991Asn (p.S991N) Consequence : Missense	Unaffected	Unaffected
5	PNDM	Sulfonylurea therapy	Gene : *KCNJ11* Location : Exon 1 DNA Description : c.175G>A Protein Description : p.Val59Met (p.V59M) Consequence : Missense	Unaffected	Unaffected
6	PNDM	Sulfonylurea therapy	Gene – *KCNJ11* DNA Description : c.136C>T Protein Description : p.(His46Tyr) Consequence : Missense	Unaffected	Unaffected
7	PNDM	Sulfonylurea therapy	Gene : *KCNJ11* Location : Exon 1 DNA Description : c.136C>T Protein Description : p.(His46Tyr) Consequence : Missense	Unaffected	Unaffected
8	PNDM	Sulfonylurea therapy	Gene – *KCNJ11* Zygosity – heterozygous HGVS description – NM_000525.3:c.175G>A.p(Val59Met) Location – Chr11:g.17409464 Classification - pathogenic	Unaffected	Unaffected
9	PNDM	Sulfonylurea therapy	Gene – *ABCC8* DNA Description : c.265C>T Protein description : p.Arg89Cys (p.R89C) Consequence : Missense	Heterozygous	Single mother
10	PNDM	Insulin therapy	Gene : *ABCC8* Location : Exon 38 DNA Description : c.4568T>A Protein Description : p.(Val1523Glu) Consequence : Missense	Affected	Heterozygous
11	PNDM	Sulfonylurea therapy	Gene - *ABCC8* Zygosity - Heterozygous Inheritance - Maternal HGVS description - NM_001287174.1: c.970G>Ap.(Val324Met) Location -Chr11:g.17482076C>T	Heterozygous	Unaffected

			Classification - Pathogenic		
12	PNDM	Insulin therapy	Gene : *GCK* Location : Exon 5 DNA Description : c.562G>A Protein Description : p.Ala188Thr (p.A188T) Consequence : Missense	Unaffected	Unaffected
13	PNDM	Deceased	Gene : *EIF2AK3* Location : Exon 13 DNA Description : c.2588T>G Protein Description : p.Leu863Ter (p.L863*) Consequence : Nonsense	Heterozygous	Non paternity
14	PNDM	Insulin therapy	Gene : *EIF2AK3* Location : Exon 14 DNA Description : c.2972G>A Protein Description : p.Ser991Asn (p.S991N) Consequence : Missense	Heterozygous	Heterozygous
15	PNDM	Deceased	Gene : *FOXP3* Location : Exon 12 DNA Description : c.1236G>C Protein Description : p.Glu412Asp (p.E412D) Consequence : Missense	Heterozygous	Non paternity
16	PNDM	Insulin therapy	Gene : *INS* Location : Exon 3 DNA Description : c.265C>T Protein Description : p.Arg89Cys (p.R89C) Consequence : Missense	Unaffected	Unaffected
17	PNDM	Insulin therapy	Gene : *INS* Location : Exon 3 DNA Description : c.265C>T Protein Description : p.Arg89Cys (p.R89C) Consequence : Missense	Unaffected	Unaffected
18	PNDM	Insulin therapy	Gene - *INS* DNA Description : c.149G>A Protein Description : p.Arg50Gln (p.R50Q) Consequence : Missense	Heterozygous	Heterozygous
19	PNDM	Lost to follow up	Where all other genetic causes have been ruled out by sequencing, neonatal diabetes in patients with Down Syndrome is aetiologically caused by trisomy 21. This recently recognised subtype of neonatal diabetes is autoimmune but is not HLA associated.	Not checked	Not checked
20	PNDM	Insulin therapy	No mutation identified	Not checked	Not checked
21	TNDM	Off drugs	Gene - *ABCC8* Location : Exon 8 DNA Description : c.1238C>G Protein Description : p.Thr413Ser (p.T413S) Consequence : Missense	Heterozygous	Unaffected
22	TNDM	Off drugs	Gene - *INS* Zygosity – Homozygous Inheritance – Biparental HGVS description – NM_001185098.1:c.-3 Location: GRCh37 (hg19)17A>C, p.? Chr11:g.2182518 Classification – uncertain significance	Heterozygous	Heterozygous
23	TNDM	Off drugs	Partial hypomethylation at the Transient Neonatal Diabetes (TND) locus. This finding is consistent with a diagnosis of TND caused by a duplication of *6q24* of paternal origin.	Not checked	Not checked
24	TNDM	Off drugs	Methylation specific MLPA – Loss of methylation of the PLAGL1 DMR Dosage analysis – Normal dosage Informative markers tested • D6S1668 (6P25.1) • D6S1721 (6p24.1) • D65S1595 (6q15) • D6S280 (6q13) Maternal loss of heterozygosity for all Interpretation – Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) detected loss of methylation at the PLAGL1 Differentially Methylated Region (DMR) in the patients DNA sample. Microsatellite analysis showed no maternal contribution for 4 polymorphic chromosome 6 markers. The other 9 loci were not fully informative, but the patient was homozygous for all of them, consistent with uniparental disomy. This result confirms a diagnosis of	Not checked	Not checked

			transient neonatal diabetes, very likely due to paternal uniparental disomy at the *624* locus.		
25	TNDM	Off drugs	Gene - *ZFP57* resulting in hypomethylation at the maternal 6q24 locus. Zygosity - Homozygous Inheritance - Biparental HGVS description -NM_001109809.2:c.844C>T p.(Gln282*) Location - Chr6:g.29641044 Classification – pathogenic	Heterozygous	Heterozygous

Figure 1. Genetic etiology of the PNDM cohort PNDPNDM cohort

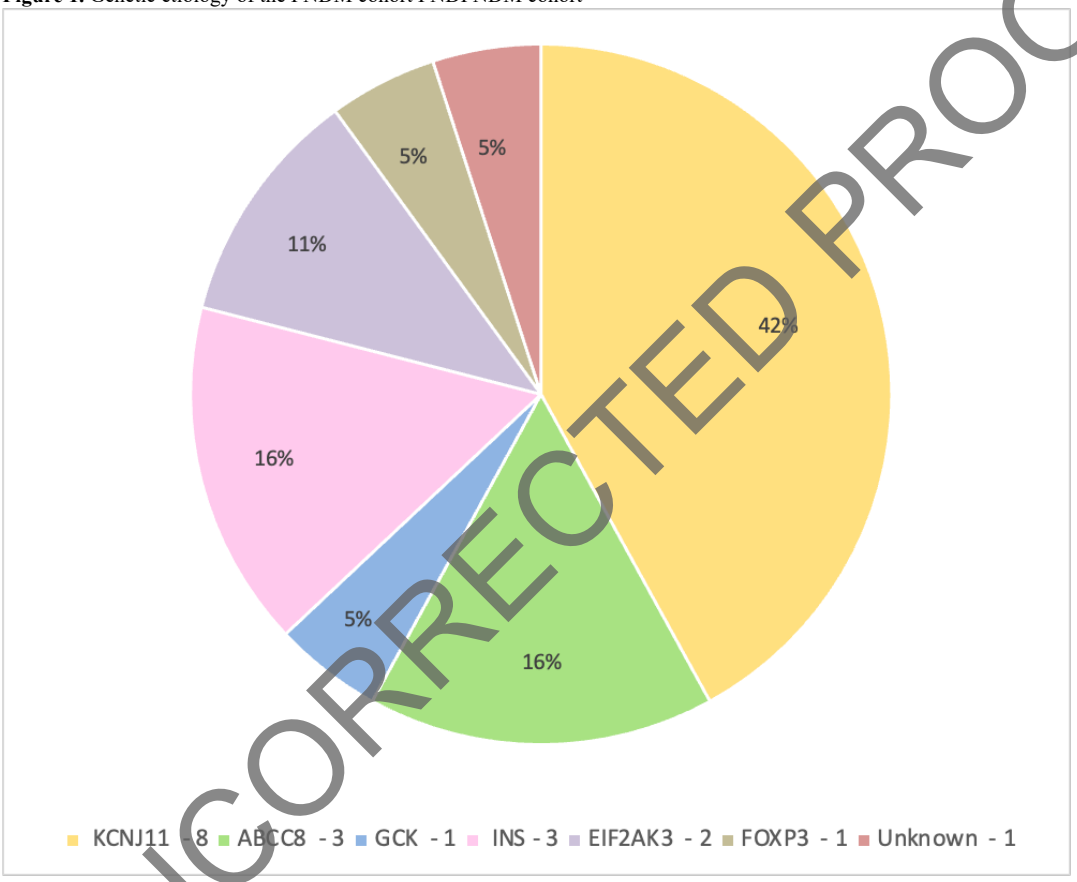

Figure 2. Age at presentation