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Diabetes Mellitus Under The Age Of One Year: Clinical Pattern, Etiological Factors And Possible Mutation In KCNJ11 Gene Encoding Of Adenosine Tri-Phosphate Sensitive Potassium Channel Gene (Kir6.2) Among Egyptian Infants

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Abstract:

Background& aim: Infantile onset diabetes mellitus (IODM) is not uncommon metabolic disorder in children, with rising in the incidence in the last few years. This research is to study clinical pattern of infantile diabetes, etiological factors and possibility of being monogenic versus type 1 diabetes mellitus through laboratory and genetic study.
Patients& methods: A descriptive study includes 50 diabetic patients with disease onset under the age of one year. Detailed medical history was taken from patients' parents and complete clinical examination. All patient subjected to laboratory investigation include HbA1C, fating C peptide, islet cell AB and inulin autoantibody. Genetic testing was done for mutations in EIF2AK3, KCNJ11, ABCC8, INS, FOXP3, GATA4, GATA6, GCK, GLIS3, HNF1B, IER3IP1, PDX1, PTF1A, NEUROD1, NEUROG3, NKX2-2, RFX6, SLC2A2 for all patients diagnosed < 6m, and SLC19A2, STAT3, WFS1, ZFP57 using targeted next-generation sequencing (NGS) panel. Sequence analysis of KCNJ11 and INS genes by Sanger sequencing were done for patients from 6-9m age at diagnosis of diabetes.
Results: The rate of DKA at time of presentation was 90%. Islet cell and insulin autoantibodies were negative in 36 (72%) patients and positive in 14 (28%) patients. Fasting C peptide was low in 74%. Genetic study could not detect genetic cause
Conclusion: Infantile onset diabetes mellitus (IODM) is uncommon but with rising incidence in the last few years. IODM diagnosis and management is challenging, late diagnosis due to lack of awareness among pediatrician that DM may occur at any age or due to lack of typical manifestations of DM (polyuria, polydipsia, weight loss) is associated with high morbidities and mortalities.

Keywords: Infantile onset diabetes mellitus (IODM), Type 1diabetes mellitus (T1DM), Neonatal diabetes mellitus (NDM).

Introduction

Type 1 diabetes mellitus is the most common type of DM in children accounting for two thirds of new cases in children of all ethnic groups[1] and the incidence has recently been increasing, particularly in children < 5 years.[2]DM diagnosed during the first one year of life is an uncommon form of diabetes that differs from the disease in older children regarding its causes, clinical characteristics, treatment options and needs for education and psychosocial support. Early recognition of diabetes in this age group can prevent the high morbidity and mortality associated with this disease.[3] IODM is differ from NDM that occur usually within first six months of life as it has different causes and may be monogenic (NDM), T1DM, developmental disorders of pancreas or syndromic.[4]

Neonatal DM is defined by the persistent hyperglycemia that requiring treatment with reported incidence according to different authors is one case per 100,000, 300,000 or even per 500,000 live births**.**[5] NDM is classified into transient (TNDM), permanent (PNDM), and syndromic forms.[6] TNDM usually resolves before 18 months of age but may reappear in early childhood.[3]About 80 percent of NDM cases had a known genetic diagnosis, There are over 20 known genetic causes for NDM.[7]Approximately two thirds of cases of TNDM are caused by abnormalities in an imprinted region on chromosome 6q24, while the majority of remaining cases caused by activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (KATP) channel of the β-cell membrane (KCNJ11 or ABCC8). A minority of cases of TNDM is caused by mutations in other genes, including HNF1B, INS.[8] PND may be either isolated or form part of a syndrome, such as Wolcott-Rallinson syndrome due to mutations in the EIF2AK3 gene, pancreatic agenesis due to mutations in IPF-1 gene and ND with cerebellar agenesis due to mutations in the PTF-1A gene. The most common cause of isolated PNDM are mutations in the genes that encode insulin (INS) and the K_{ATP} channel (KCNJ11 and ABCC8).[9] So activating heterozygous mutations in the genes encoding either subunit of the ATP-sensitive potassium channel (KATP channel; KCNJ11 or ABCC8) of the pancreatic beta-cell are the most common cause of permanent neonatal diabetes, and the second most common cause of transient NDM, Combined, these mutations account for more than 50% of all cases of NDM.[10]Most patients with mutations in KCNJ11 and ABCC8 are responsive to sulfonylurea therapy and can be transitioned from insulin to sulfonylurea (SU) therapy after the genetic tests have done.[5]

- Little is known about DM during infancy and with increasing incidence of newly diagnosed, so we decide to study these patients as regarding clinical pattern, etiological factors and detect whether these cases are monogenic versus type 1 diabetes mellitus.

Patients& methods

Study setting & design:

This descriptive cross sectional study performed in Pediatric Endocrinology Unit at Assuit University Children Hospital (AUCH) in Egypt, from January 2017 to December 2021 on 50 patients diagnosed with diabetes under the age of one year. The diagnosis of DM was made using the International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines[11]
It was approved by the institutional review board of Assuit faculty of medicine and was in accordance with the 1964 Helsinki declaration and its later amendments with approval number **IRB**: 17200037. The study was registered at clinical trial. gov as ID: **NCT03519217**. Informed written consents were obtained from the patients' parents to conduct and publish this research.

Sample size calculation

Based on determining the main outcome variable (Percentage of NDM with gene mutation; KCJN11), the calculated total sample size is 52. The sample size was calculated using G*power software 3.1.9.2., based on the following assumptions: Main outcome variable is:

Percentage of NDM with gene mutation; KCJN11. Previous studies reported that among children with NDM admitted to hospital settings, the percentage of children diagnosed with KCJN11 gene mutations ranged between 37.5% (Hashimoto et al., 2017).

Patient identification

Inclusion criteria

This study enrolled patients with newly diagnosed diabetes mellitus under the age of one year.

Exclusion criteria:

- Diabetic children with the disease onset above the age of one year.
- Infants with stress hyperglycaemia.
- Secondary DM

Methodology

-Clinical details of patients were obtained and including age of onset, date of diagnosis, presentation, gestational age, birth weight, maternal disease during pregnancy, intensive neonatal care admission, neonatal jaundice, mode of delivery, multiple gestations, maternal age, maternal weight at pregnancy, socioeconomic status, type of feeding (breast feeding, artificial feeding (type of milk), weaning onset include type of food, vitamin D supplementation, family history of diabetes, weight, length, general features, and systematic examination.

-Laboratory investigations were done and include basal investigations (complete blood picture, liver function test for patients with hepatomegaly) HbA1C, fasting C peptide, anti-insulin and anti-islet autoantibodies.

-Pelvi-abdominal ultrasound was done for all patients.

Genetic analysis

DNA samples from patients were isolated from peripheral blood in laboratories of Assuit University Hospitals followed by extraction and purification according to the manufacturer's protocol (QIAamp DNA Blood Maxi Kit, Qiagen, Cat. No.: 51194). DNA concentrations were measured by Qubit 4 fluorometer with use Invitrogen (by Thermo Fisher scientific) Qubit 1ds DNA HS Assay Kit, and concentration results of patients were range from 15-88 ng/ml.

Genetic testing was performed in Exeter Genomics Laboratory, Exeter (UK) according to De Franco et al., 2015 [6]. Briefly, rapid Sanger sequencing of the ABCC8, KCNJ11, INS, and EIF2AK3 genes was performed for patients diagnosed with DM less than 6m age, patients who did not have a pathogenic variant in one of these genes were then tested using custom targeted next-generation sequencing (NGS) assay, covering the coding regions and conserved splice sites of the KCNJ11, ABCC8, INS,EIF2AK3, FOXP3, GATA4, GATA6, GCK, GLIS3, HNF1B, IER3IP1, PDX1, PTF1A, NEUROD1, NEUROG3, NKX2-2, RFX6, SLC2A2, SLC19A2, STAT3, and WFS1 genes. This assay can also detect partial/whole gene deletions and duplications. [12] Variant classification was performed using the latest version of American College of Medical Genetics and Genomics (ACMG) best practice guidelines.[13] Sequence analysis of KCNJ11 and INS genes by Sanger sequencing were done for patients from 6-9m age at diagnosis of diabetes.

Statistical analysis

Data were verified, coded by the researcher, and analysed using SPSS version 24*. Descriptive statistics: Means, standard deviations, medians, ranges, and percentages were calculated. Test of significances: for categorical variables; chi-square/ Fisher's/Monte Carlo Exact test was used to compare the frequency between groups. For continuous variables, independent t-test analysis was carried out to compare the means. A p-value equals or less than 0.05 was considered significant.

Results:

1. Demographic data and clinical history:

In our study the incidence of IODM constitutes 5.8% of all diagnosed patients with DM up to17 y old at the same period. The mean age at diagnosis was10.38± 2.4 months with range 3 – 12m with male to

female ratio was 1.2:1. There was significantly higher DM occurrence in rural areas than in urban areas (72% vs 28%). Positive family history of DM among studied population was found in 24% of patients and most of them were among first degree relatives. The rate of consanguinity in the studied cases was 50% all of them among second degree. In terms of obstetric history, 56% of patients had delivered by CS with statistically significant higher incidence of CS (73.3%) among patients diagnosed as T1DM (with positive autoantibodies) with P value 0.045. Most of patients were full term (98%). Mean BW among studied population was 2.87 ± 0.6 kg. Most of studied populations in present study were exclusive breast fed (78%).

2. Clinical presentation

The majority of the patients (90 %) were initially diagnosed with diabetic ketoacidosis (DKA) with 60% had severe DKA (pH<7.1 or bicarbonate <5mmol/L , Kussmaul or depressed respirations; sleepy to depressed sensorium to coma). Two patients had history of polyuria, and three patients had persistent diaper rash. There was high incidence of misdiagnosis (74%) among studied population, and initially diagnosed as acute CNS infection, septic shock, bronchopneumonia, bronchiolitis or diarrheal dehydration. Hepatomegaly was found in 32% studied patients. All patients with hepatomegaly had normal liver function tests except one patient that had raised liver enzymes and had features consistent with Fanconi Bickle syndrome. One patient had developmental delay and epilepsy and one patient had multiple autoimmune disease (celiac, hypothyroidism) which developed after few month of DM diagnosis. 12% of patients were short.

3. Laboratory investigations

Laboratory investigations including CBC, liver function test (for patient with hepatomegaly), random blood glucose, C-peptide, HbA1c, islet cell and antiinsulin antibodies are shown in Table 3.

The mean HbA1C for studied population was 9.45 ± 1.5 5%.

Islet cell and insulin autoantibodies were positive in 14 patients (28%). Fasting C peptide was low in 74% of studied population with the mean 0.74 ± 1.2 ng/ml, normal in 18% and high in 8% of patients.

4. Genetic testing

Genetic study could not detect genetic cause among patients who tested for genetic abnormalities.

Discussion:

In our study the incidence of IODM constitutes 5.8% of all diagnosed patients with DM at same period up to age of 17 y old in Pediatric Endocrinology Unit, AUCH. Similarly IODM constitutes 6.1% among newly diagnosed children with DM admitted in Pediatric Endocrinology Unit, AUCH by Mohamed et al 's study within one year from 2016 to 2017[14]. Data about incidence of infantile diabetes in Egypt is deficient, A study was done in Egypt by El-Ziny et al and included all DM patients aged 0-18 years and reported that from a total of 1600 DM patients, the patients diagnosed within first 2ys of life account for 3.6% of total patients[15]. In another study conducted at Aswan University Hospital by **Abd El-Moneim** et al, the incidence of DM among infant (<2y) was 20% of all studied population[16]. In similar study done in India by Varadarajan et al, they found that over a period of 12.5 years from 1999 to 2012, 506 diabetic children aged less than 12 years of whom 40 (7.9 %) children were IODM i.e., diagnosed at age less than one year [17]. The difference in reported percentage among different studies may be attributed to the different durations of the studies, different age groups included and different definitions of IODM.

The mean age at diagnosis was 10.38± 2.4 month, with range 3 – 12m. It was slightly higher to other similar study done by Abdelmeguid et al[(18)], on infantile diabetes in Alexandria University where the mean age at time of diagnosis was 7.9±3.8 months, and it was higher than a study done

in India on infantile diabetes by Varadarajan et al [19] where the age range was from 3 days to 12 months with mean 3.75± 2.6 months . This may be due to lower number of cases diagnosed less than 6m (8%) in our cohort compared to 70% in Varadarajan et al's study, and 30.7% in Abdelmeguid et al's study. Also late diagnosis may be the cause of higher mean of age of diagnosis in this study; as evidenced by high mean of HbA1c 9.45 ± 1.5 and high rate of misdiagnosis among studied cases (74%).

Among the studied cases, male to female ratio was 1.2:1. This was similar to what reported by other studies [18 ,19]. The near similar frequency of IODM among males and females may be attributed to the fact that monogenic diabetes have different mode of inheritance (AD,AR) or denovo mutation with no sex predilection as well as T1DM where many studies had been done on incidence and prevalence of T1DM in the younger age group (children 0–4 years of age) show no gender differences [20,2122].

In this study, there was significantly higher DM occurrence in rural areas than in urban areas (72% vs 28%). This is similar to a study done in Nile Delta, Northern Egypt by El-Ziny et al[15]included all DM patients aged 0-18 years in which the prevalence of diagnosed patients with DM in rural areas estimate 85.4%.This may be attributed to the nature of our community (Upper Egypt) and in Nile Delta region of Egypt in which most of population in these regions are living in rural areas which is supported by the reported data from Ministry of Health and Population at 2017 [23].

The rate of consanguinity in the studied cases was 50% and it was higher than a study done by Abdelmeguid et al[18], on infantile diabetes in Alexandria University where the rate of consanguinity was 23.1%, also higher than in a similar study done in India by **Varadarajan et al** [17] where the rate of consanguinity was 30%. This may be explained by the high rate of consanguineous marriage in Upper Egypt specially among rural residence and this is supported by study done on rate of consanguineous marriage in Egypt by Ahmed SM.[24]

Positive family history of DM among studied population was found in 24%, this lower than what reported by Abdelmeguid et al (33.3%). [18]

The clinical presentation of diabetes at this younger age group is somewhat differ from those with older age. In the present study, the rate of DKA at time of diagnosis was 90% of studied patients and among them 60% had severe DKA. Classical symptoms of diabetes (polyuria, polydipsia and weight loss) were not the presenting complaint in most of the cases. Among the 50 infants, no deaths occurred at initial diagnosis. Need for hospitalization existed for all of the diabetic infants at initial diagnosis. Recurrent hospital admissions occurred for most of cases during follow up for severe metabolic derangements (Hypoglycemia or DKA) or intercurrent infection. This result was similar to what reported by Abdelmeguid et al[18], who found that 92.3% of studied infantile diabetes cases presented with DKA. Also a high prevalence of DKA (67.5%) at time of presentation among diabetic infant in study done in India by **Varadarajan et al** [17]. This can be explained by lack of awareness among physicians that DM can present at this young age even during neonatal period; this is supported by high incidence of misdiagnosis (74%) among studied population. Initial diagnosis in the study group included acute CNS infection, septic shock, bronchopneumonia, bronchiolitis or diarrheal dehydration. Also in **Varadarajan et al** [17 study, 67.5% of cases misdiagnosed initially. On the other hand, a study done in Turkey by Öngen et al[25] on 16 diabetic infants, found that the rate of DKA at time of diagnosis was lower than our study (56. 25%) and this may be due to lower sample size at that study and it was retrospective study and the clinical data were obtained from medical records.

The common co-morbid conditions among studied patients were hepatomegaly in 32%. All patients with hepatomegaly had normal liver function tests except one patient that had raised liver enzymes and had features consistent with Fanconi Bickle syndrome (Massive hepatomegaly, rickets, and failure to thrive), liver biopsy confirmed the diagnosis of glycogen storage disorder and died suddenly after 1

year of diagnosis but genetic study did not show mutation in SLC2A2 gene. Microcytic hypochromic anemia was found in 32% of patients. Neurological deficit (Developmental delay/Epilepsy) was found in one patient who is a product of consanguineous marriage (cousin) and had history of NDM in another sibling, this consistent with DEND syndrome. One patient had multiple autoimmune disease (DM at age of 7m, hypothyroidism at age 9m and celiac disease at age 11 m), but without gene mutation in FOXP3, STAT3, or LRBA, so HLA typing and assessment of T1DM-GRS is recommended. None had pancreatic hypoplasia or aplasia by ultrasonography of the abdomen. Total daily insulin dose used initially for IODM in our study range from 0.3 – 0.9U/kg with a mean 0.61U/Kg of intermediate acting or long acting insulin to avoid hypoglycemia associated with short acting insulin. Use of continuous subcutaneous insulin infusion may be an ideal option to deliver smaller doses of insulin[26]. This result is much lower than that reported by **Varadarajan et al** [17] where the total daily insulin dose ranged from 0.35-3U/kg and that reported by Abdelmeguid et al[18], where the total daily insulin dose ranged from 0.4- 1.2 U/kg. The difference in total insulin dose used in our study and other similar studies may be due to different types of insulin used, different causes of DM and different body weight of patients. The major problem encountered during management in all infants was maintaining glycemic control because their insulin requirement was minimal and there was difficulty in giving small doses of insulin, erratic feeding habits, difficulty in monitoring serum glucose levels, parental unawareness of the condition, and complications encountered, especially hypoglycemia.

The mean HbA1C at diagnosis for studied population was 9.45 ± 1.5 5%. Similarly, the mean HbA1C at diagnosis in patients with IODM in Alexandria University was 9 ± 2 % in Abdelmeguid et al[18] study.

Islet cell and insulin autoantibodies had been done for all patients and showed that 14 patients (28%) were positive (10 patients (20%) were positive for anti-islet cell Ab only, 2 patients (4%) were positive for anti-inulin Ab only and 2 patients (4%) were positive for both). Among patients diagnosed ≤9 m age 20% (3/15) were autoantibodies positive, all of them diagnosed between 6-9m and had positive family history of T1DM among first degree relatives and other family members and suggesting diagnosis of T1DM, while those diagnosed between 9-12 m age 31.4% (11/35) were autoantibodies positive. In contrary to Abdelmeguid et al's [18] study, in which all studied diabetic infants were negative for anti-islet cell Ab, and 38.5% were positive for antiGAD-65 Ab and 7.7% were positive for anti-insulin Ab. They found that most of the patients with positive antiGAD-65 Ab were diagnosed between 6-12 months (51.9%), whilst only one patient < 6m (8.3%) was positive (with a statistically significant difference (P value 0.013) while ant insulin Ab showed no statistically significant difference with the disease onset. As regarding autoantibodies pattern in diabetic infants that possibly have T1DM, many studies had been done on prevalence of autoantibodies in children with newly diagnosed T1DM, in Albuhairan et al's study in Saudi Arabia showed that 67% were positive for ICA, 36% for IAA and 84.4% for GAD, and the presence of ICA was predominant in children aged under six years[27].In another large study done in Germany by Scherbaum et al showed that among patient from 0-5y the prevalence of ICA was 87.5% and antiGAD was 25%[28]. Many studies have suggested that autoantibodies are usually negative in NDM patients diagnosed before six months of age, except for maternal autoantibodies, which may have crossed the placenta and patients with monogenic autoimmunity such as IPEX syndrome.[25'29]However in a large study done by Hattersley et al[30], they found that infants with a high type 1 diabetes genetic risk score (T1D-GRS) had a similar rate of autoantibody positivity to that seen in infants with type 1 diabetes diagnosed at 6–24 months of age (41% vs 58%, p = 0.2).

Fasting C peptide was low in 74% of studied population with the mean was 0.74 ± 1.2ng/ml. Our result is higher than that reported by Abdelmeguid et al's [18] study

in which the mean of C peptide was 0.2 ± 0.2 ng/ml, this may be due to using different type of commercially available kits.

Genetic study was done and showed that all patients diagnosed < 6m could not detect genetic cause including the 26 known genes of NDM and genetic study done to patients between 6-9 m for most common genetic cause at this age group (INS, KCNJ11) and could not detect genetic abnormalities. Diabetes that presents in the first 6 months of life (NDM) has been thought to be exclusively caused by a pathogenic variant in a single gene; nearly 85-90% of individuals have gene mutation in one of known 26 genes of NDM, the remaining ~10–15% may have a causative pathogenic variant in a gene or non-coding region that has not yet been identified[30]. Another possibility is that they have polygenic T1DM and represent the extreme tail of the distribution of presenting age of type 1 diabetes[30].

In conclusion, the rate of DKA at time of presentation 90% among studied patients, with 60% had severe DKA; this was due to high rate of misdiagnosis that represents 74%. Islet cell and insulin autoantibodies had been done for all patients and showed that 36 (72%) patients were negative and 14 (28%) were positive for autoantibodies (10 patients (20%) were positive for anti-islet cell Ab only, 2 patients for anti-insulin Ab (4%) only and 2 patients positive for both). Also genetic study was done in our cohort in trying to detect possible underlying genetic cause of DM among studied population for all patient diagnosed < 6m including the 26 known genes of NDM and could not detect genetic cause and genetic study done to patients between 6-9 m for most common genetic cause at this age group (INS, KCNJ11) and could not detect genetic abnormalities. Positive family history of T1DM among studied population was found in 24% of patients.

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Table 1: Demographic data, history, and initial presentation of the studied patients:

Variable	Category	n = 50
Age at Diagnosis	• **Mean ± SD**	10.38 ± 2.4
	• **Median (Range)**	12 (3 – 12)
Sex	• **Female**	22 (44%)
	• **Male**	28 (56%)
Residence	• **Urban**	14 (28%)
	• **Rural**	36 (72%)
SES	• **Low**	20 (40%)
	• **Moderate**	23 (46%)

	• **High**	7 (14%)
Maternal Age at Pregnancy/years	• **Mean ± SD**	28.46 ± 5.7
	• **Median (Range)**	29 (16 – 40)
Maternal Disease during Pregnancy	• **No**	45 (90%)
	• **GDM**	3 (6%)
	• **Pre-eclampsia**	2 (4%)
Maternal Smoking	• **No**	32 (64%)
	• **Yes (Passive)**	18 (36%)
Mode of Delivery	• **Normal**	22 (44%)
	• **CS**	28 (56%)
Gestational Age	• **Full term**	49 (98%)
	• **Preterm**	1 (2%)
Birth Weight	• **Mean ± SD**	2.87 ± 0.6
	• **Median (Range)**	3 (2 – 4.5)
	• **Low BW**	7 (14%)
	• **Appropriate BW**	40 (80%)
	• **High BW**	3 (6%)
Vit D Supplementation	• **No**	21 (42%)
	• **Regular**	16 (32%)
	• **Irregular**	13 (26%)
NICU Admission		7 (14%)
Cause of NICU Admission	• **Neonatal Jaundice**	5 (10%)
	• **RDS**	2 (4%)
	• **Low Birth Weight**	1 (2%)
Neonatal Jaundice	• **Yes**	19 (38%)
Phototherapy	• **Yes**	5 (10%)
FH Type 1 DM	• **Yes**	12 (24%)
	• **DM 1st degree**	7 (14%)
	• **DM 2nd, 3rd degree**	5 (10%)

Consanguinity		
	• **2nd**	20 (40%)

SD: standard deviation, SES: socioeconomic state, GDM: gestational diabetes mellitus, CS: cesarean section, SIDS: sudden infant death syndrome, BW: birth weight, NICU: neonatal intensive care unit, RDS: respiratory distress syndrome, FH: family history, DM: diabetes mellitus, DKA: diabetic ketoacidosis, FU: follow up.

Table 2: Comorbidities of the studied sample

Variable	Category	n = 50
Comorbidity	• **Hepatomegaly**	16 (32%)
	• **CBC abnormality (MHA)**	16 (32%)
	• **Liver function abnormality**	1 (2%)
	• **Neurological deficit (Developmental delay/Epilepsy)**	1 (2%)
	• **Celiac Dis./Hypothyroidism**	1 (2%)

MHA: microcytic hypochromic anaemia.

Table 3: Laboratory Investigation Data of the studied sample

Variable	Category	n = 50
HbA1C (%)		16 (32%)
	• **Mean ± SD**	9.45 ± 1.5
	• **Median (Range)**	10 (6.8 – 13)
Fasting C Peptide (ng/ml)	• **Mean ± SD**	0.74 ± 1.2
	• **Median (Range)**	0.34 (0.01 – 7.3)
	• **Low (< 0.78)**	37 (74%)
	• **Normal (0.78-1.89)**	9 (18%)
	• **High (> 1.89)**	4 (8%)
IAA	• **Mean ± SD**	3.36 ± 3.1
	• **Median (Range)**	1.5 (0.13 – 26.8)
Islet Cells auto-Ab and Insulin auto-Ab		
	• **Islet Cells auto-Ab (Positive)**	10 (20%)
	• **Insulin auto-Ab (Positive)**	2 (4%)
	• **Both Negative**	36 (72%)
	• **Both Positive**	2 (4%)

SD: standard deviation**,** IAA: inulin autoantibody**, Ab: antibody.**

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