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ORIGINAL ARTICLE

Characteristics of Children with Newly Diagnosed Type 1 Diabetes Mellitus in Brunei Darussalam

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Abstract

Objective. This study aims to characterize the presentation, biochemical status of children with T1DM at diagnosis, the type of subcutaneous insulin regimens initiated, and to determine the incidence of T1DM in Bruneian children aged 18 years and younger.

Methodology. A retrospective electronic and paper medical chart review was performed on patients aged 18 years and younger diagnosed with T1DM from 2013 to 2018 in Brunei Darussalam.

Results. A total of 31 children with a mean age of 10.2 ± 3.6 years old were diagnosed with T1DM, of which 66.7% presented with diabetic ketoacidosis (DKA), a majority in severe DKA with an intercurrent illness (p = 0.021). The mean HbA1c was 13.6 ± 2.7% with a mean serum glucose of 37.0 ± 14.9 mmol/L at diagnosis. In the majority of the children (67.7%), multiple daily injections of subcutaneous insulin were initiated. The incidence of T1DM in children aged 18 years and younger was 4.9 per 100,000 for the year 2018.

Conclusions. The majority of the patients in this study presented with severe DKA with an intercurrent illness. This highlights the importance of childhood T1DM awareness among the public and healthcare providers. The incidence of childhood T1DM in Brunei Darussalam is similar to other countries in the Asian region, being relatively low, compared to the rest of the world.

Key words: type 1 diabetes mellitus, diabetic ketoacidosis, pediatric

INTRODUCTION

Globally, type 1 diabetes mellitus (T1DM) is the most common type of diabetes affecting children and adolescents.[1,2] Symptoms of T1DM in children are often vague and T1DM may initially present with an intercurrent illness, which renders arriving at an accurate diagnosis challenging.[2-6] Several studies have shown that the mean duration of symptoms prior to diagnosis is over 2 weeks with a significant number of children experiencing delay in diagnosis or misdiagnosis and only one in five is diagnosed correctly during their first encounter with a physician.[7,8] Often, there is a concurrent illness noted in young children at diagnosis, causing an acute metabolic decompensation leading to diabetic ketoacidosis (DKA), which has immediate life-threatening implications and is associated with poorer long-term diabetic control.[9-11] Hence, early identification is important in preventing the morbidity and potential mortality associated with new-onset diabetes in this vulnerable age group.[9]

Multiple epidemiological studies have demonstrated that the incidence of T1DM is on the rise around the world;[3-5] however, there are currently no published data on the incidence of pediatric T1DM in Brunei Darussalam. In the Asian region, the incidence of T1DM is relatively low compared to the rest of the world, at approximately 2 to 5 per 100,000 person-years.[12,13] In neighboring Singapore, the incidence of Type 1 diabetes in children aged 0-12 years is 2.46 per 100, 000 children.[13] Meanwhile, according to the Malaysian Diabetes in Children and Adolescents Registry, 71.8% of children with diabetes mellitus in Malaysia under the age of 20 years had T1DM with more than half of the patients (58.3%) presenting with DKA at diagnosis.[14]

The objectives of this study are to characterize the presentation, family history, and biochemical status at the time of diagnosis of T1DM, and to determine the incidence of T1DM in Bruneian children. Additionally, the study aims to determine the type of subcutaneous insulin regimens initiated for these children.

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METHODOLOGY

All children aged 18 years and younger who were diagnosed with new-onset T1DM from 1st January 2013 to 31st December 2018 in Brunei Darussalam were identified through an extensive computerized search from the complete list of the ICD-10 codes for T1DM (E10.X) in Bru-HIMS (Brunei Darussalam Healthcare Information and Management Systems) and a nationwide pediatric clinic database of pediatric patients on follow-up for diabetes mellitus in all government hospitals in Brunei Darussalam. The extensive list of ICD-10 codes is included in Appendix 1. Bru-HIMS is an electronic health record system in which all Bruneian patients are mandated to register where their health information are collected under one patient record. This was officially launched nationwide on September 11, 2012. It is a nationwide population-based healthcare database and the capture rate is almost 100% as it is used in all government hospitals, outpatient services, treatment centers and clinics in Brunei Darussalam. Bru-HIMS is not available though in private clinics and hospitals. Still, all children with T1DM are eventually referred to government hospitals for management and continuation of care. This is because Brunei is a small country, and there is only one main tertiary hospital that can provided appropriate intensive care and diabetes care for pediatric patients. Hence, the capture rate for all children diagnosed with T1DM is high through Bru-HIMS.

A systematic, retrospective electronic medical chart review was performed for all children aged 18 years and younger with new-onset T1DM between 2013 and 2018. Data extracted from paper and electronic patient records included demographic, clinical and biochemical details. Information including symptoms of weight loss, polyuria, polydipsia, nocturia and presence of any intercurrent illness (such as viral gastroenteritis or cellulitis) at the time of diagnosis of T1DM were collected. Having a first-degree relative with T1DM or T2DM (type 2 diabetes mellitus) was considered as a positive family history. DKA was defined as hyperglycemia with serum glucose ≥11.1 mmol/L, venous pH <7.30, and/or serum bicarbonate <15 mmol/L in the presence of ketones.[15,16] Furthermore, the severity of the DKA was categorized as "Mild": Venous pH <7.3 or serum bicarbonate <15.0 mmol/L, "Moderate": Venous pH <7.2, serum bicarbonate <10.0 mmol/L, or "Severe" Venous pH <7.1, serum bicarbonate <5.0 mmol/L.[15,16] In addition, the type of subcutaneous insulin regimen prescribed subsequently: twice daily insulin (intermediate acting with short acting insulin) or multiple daily injections (long-acting insulin once daily with pre-meal short acting insulin three times per day), were also recorded.

All patient information were de-identified and recorded into a password-protected research database. During data extraction, each case was examined carefully to ensure that patients who were older than 18 years at the time of diagnosis or who had other types of diabetes mellitus besides T1DM such as type 2 diabetes mellitus, diabetes associated syndrome such as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness) or other causes including thalassemia -related diabetes or cystic fibrosis-related diabetes were excluded from the study. Ethical approval was obtained from the Brunei Darussalam Ministry of Health Research and Ethical Committee prior to the commencement of the study.

For statistical analysis, the data from this study were analyzed using Statistical Package for Social Sciences Program (SPSS, Version 20, IBM, Chicago, Illinois, USA). Frequency data were presented as mean ± standard deviation. Laboratory data were stratified by metabolic status (DKA or non-DKA at presentation) with mean ± standard deviation. Fisher's exact test was carried out for variables with less than 5 expected entries in more than 20% of the cells. A p-value of <0.05 was used as a cut-off for all tests to ascertain statistical significance.

The incidence of T1DM in children aged 18 years and younger was calculated by dividing the total number of new T1DM cases by the population consisting of 18 years and under in Brunei Darussalam for that year. We acquired the information on the number of children aged 18 years and younger in Brunei Darussalam through the Brunei Department of Economic Planning and Development.[17]

RESULTS

A total of 31 children were newly diagnosed with T1DM from 2013 to 2018 in Brunei Darussalam. The mean age at the time of diagnosis of T1DM was 10.2 ± 3.6 years with a near equal distribution between males and females. In terms of ethnicity, the largest proportion of patients were Malays comprising 74.2% of the study population, as it is the race of the majority of the population in the country. None of the children had a first-degree relative with T1DM, though 19.4% did have a first-degree relative with T2DM.

The children predominantly presented with classic osmotic symptoms of T1DM including polyuria in 22 patients (93.1%), polydipsia in 26 patients (92.9%) and nocturia in 20 patients (90.0%). Weight loss was also frequently reported in 72.4% of the children in our study.

A total of 21 patients (66.7%) patients presented with DKA. Majority of them, 71.4%, were in severe DKA, 23.8% in moderate DKA and the remaining 4.8% presented with mild DKA. Of significance, a larger number of children in the DKA group also had an intercurrent illness such as viral gastroenteritis and cellulitis at the time of diagnosis compared to the non-DKA group (61% versus 30%, p = 0.02). None of the children in this study had cerebral edema and there were no mortalities from DKA or T1DM.

The mean serum glucose at diagnosis was 37.0 ± 14.9 mmol/L with mean HbA1c of 13.6 ± 2.7 % though both were not statistically different between the DKA and non-DKA group. Twenty-two patients in our study had low

C-peptide levels (<370.0 pmol/L) and majority had at least the presence of one auto-antibody at presentation. As part of our routine management for newly diagnosed patients with DKA, only anti-islet cell antibodies and anti- glutamic acid decarboxylase were tested. Furthermore, 42.6% of the children in our study had abnormal thyroid function tests at the time of diagnosis (Table 1).

Different subcutaneous insulin regimens were prescribed, with 21 patients (67.7%) on multiple daily insulin injections while the remaining 10 patients (32.3%) were on the twice daily insulin injections. No patients were commenced on insulin pump therapy.

Table 1. Baseline demographics and biochemistry of all children aged 18 years and younger diagnosed with new-onset Type 1 Diabetes Mellitus from 1st January 2013 to 31st December 2018 in Brunei Darussalam

Baseline Characteristics	Mean ± SD, n (%)
Age at diagnosis in years, mean ± SD	10.2 ± 3.6
Sex, n (%)	
Male	14/30 (47.0%)
Female	14/30 (47.0%)
Race, n (%)	
Malay	23/31 (74.2%)
Non-Malays	8/31 (25.8%)
First degree relatives with T1DM, n (%)	0/30 (0%)
First degree relatives with T2DM, n (%)	6/31 (19.4%)
Symptoms at diagnosis, n (%)	
Weight loss	21/29 (72.4%)
Polyuria	27/29 (93.1%)
Polydipsia	26/28 (92.9%)
Nocturia	20/22 (90.9%)
Intercurrent illness	19/31 (61.3%)
Diabetic Ketoacidosis at presentation	21/31 (67.7%)
Serum glucose at diagnosis (mmol/L), mean ± SD	37.0 ± 14.9
HbA1c at diagnosis (%), mean ± SD	13.6 ± 2.7
Low C-peptide <370.0 pmol/L at presentation	22/29 (75.9%)
Presence of at least one autoantibody, n (%)	19/26 (73.1%)
One positive antibody	9/26 (34.6%)
Two positive antibodies	10/26 (38.5%)
Glutamic acid decarboxylase (GAD) positivity, n (%)	16/26 (61.5%)
Insulinoma-antigen 2 (IA2) positivity, n (%)	13/26 (38.5%)
Abnormal Thyroid function test, n (%)	12/26 (46.2%)

Published population data by the Brunei Department of Economic Planning and Development for children under the age of 18 years and under was only available for the year of 2018.[17] Hence, we were only able to calculate the incidence of T1DM in pediatric patients for that particular year. In 2018, the population in Brunei Darussalam was 442,400, with 27.5% of the population being aged 18 years and under.[17] There were 6 pediatric patients who were Bruneian or permanent residents of Brunei Darussalam that were newly diagnosed with T1DM for the year of 2018. Utilizing this available information, the incidence of T1DM in children aged 18 years and younger was calculated to be 4.9 per 100,000 for the year 2018.

DISCUSSION

This is the first population-based study carried out in children with T1DM in Brunei Darussalam examining the clinical and biochemical characteristics at diagnosis. During the 6-year study period, a total of 31 children aged 18 years and younger were diagnosed with T1DM. More than half of the patients in this study (66.7%) presented with DKA, predominantly with severe DKA (Table 2). This highlights the importance of early identification of children with T1DM, ideally before the development of DKA as this acute condition is associated with high morbidity and mortality. The presence of DKA at initial presentation in our cohort is comparatively higher than that reported from developed countries such as Sweden (12.8%), Finland (19.0%) and UK (25.0%) where prevalence rates of T1DM are higher.[18-21] This may be attributed to different racial and environmental factors but may also reflect the lack of public awareness of diabetic symptoms in children among the Bruneian population.

Comparable to other studies,[6-10] the children in our study also predominantly presented with the classic osmotic symptoms of T1DM such as polyuria, polydipsia and nocturia. Of significance, majority who presented with DKA also had an intercurrent illness at the time of diagnosis, which likely contributed to the acute metabolic decompensation that can lead to immediate, life-threatening

Table 2. Comparison between †DKA and Non-†DKA group

	†DKA (n = 21)	Non-†DKA (n = 10)	*p*
Sex, n (%)			
Male	9/21 (42.9%)	5/10 (50.0%)	
Female	12/21 (57.1%)	5/10 (50.0%)	1.00
Race, n (%)			
Malay	17/21 (80.9%)	6/10 (60.0%)	
Non-Malays	4/21 (19.1%)	4/10 (40.0%)	0.38
First degree relatives with T1DM, n (%)	0/20 (0%)	0/10 (0%)	-
First degree relatives with T2DM, n (%)	4/21 (19.0%)	2/10 (20.0%)	1.00
Low C-peptide levels (<370 pmol/L)	18/20 (90.0%)	5/8 (62.5%)	0.123
Presence of intercurrent illness	16/21 (61.3%)	3/10 (30.0%)	0.02*
Presence of at least one autoantibody, % (n)	12 /17 (70.6%)	7/9 (77.7%)	1.00
One positive antibody	4/17 (23.5%)	5/9 (55.6%)	0.19
Two positive antibodies	8/17 (47.1%)	2/9 (22.2%)	0.40

†DKA: Diabetic Ketoacidosis
*A *p*-value of <0.05 was used as a cut-off for all tests of statistical significance. Fisher's exact tests were carried out for variables with less than 5 entries.

complications.[7,8] The intercurrent illnesses detected were cellulitis and viral gastroenteritis that present with vague symptoms such as vomiting or abdominal pain. These illnesses can trigger DKA or mimic the acute presentation of DKA. Thus, symptoms of T1DM may be misinterpreted, leading to delayed diagnosis and significant morbidity. More concerning in the findings of our study was that some patients were already symptomatic with polyuria, polydipsia, nocturia and weight loss for up to 3 months before seeking medical attention. Such delay in pursuing medical care may have serious health implications.

In contrast to western countries where there are T1DM patients who have a positive family history [18-21], none of the children in our study had any first-degree relatives with T1DM. However, 19.4% had a first-degree relative with T2DM, which demonstrates the worrying rising trend in the prevalence of T2DM among the adult Brunei population, mostly as a consequence of sedentary lifestyle and obesity. A recent population survey demonstrated a 28% obesity prevalence and 10% T2DM prevalence in the Brunei adult population.[22]

Patients with T1DM have a higher prevalence of auto-immune diseases compared to patients without diabetes.[5] Nearly half (42.6%) of the children in our study had abnormal thyroid function tests during presentation but none had any subsequent formal diagnosis of auto-immune thyroid disorder on follow-up. This is likely attributed to non-thyroidal illness during the acute presentation.

The "basal-bolus" or the multiple daily insulin injection regimen, which mimics the physiological insulin secretion is the preferred choice for treatment, as majority (67.7%) of patients were commenced on this regimen. No patients were prescribed insulin pump therapy at discharge, due to our relative inexperience with this insulin regimen in the pediatric population, although this service has been provided in adult endocrine clinics since 2013.

The incidence of T1DM in children aged 18 years and younger is 4.9 per 100,000 for the year 2018. To our knowledge, this is the first study looking at the incidence of childhood T1DM in Brunei Darussalam. The worldwide incidence of T1DM is quite variable and the data from our study suggest that the incidence of T1DM in children in Brunei is quite low compared to the countries with the highest incidence namely Finland and Italy (36.5 and 36.8/100,000 per year, respectively).[12,21]

Our study has several limitations. The number of patients in this cohort is small given the population of Brunei Darussalam. It is also a retrospective study done through chart review which relies on the documentation of others; therefore, some clinical details may be missing from the chart. Another limitation of the study is the possibility, albeit remote, of missing data for patients' encounter at private clinics and hospitals as these are not captured in Bru-HIMS.

CONCLUSION

The result from our study demonstrated that a significant proportion of our children with T1DM presented with severe DKA at diagnosis, often accompanied by an intercurrent illness. The common symptoms of T1DM such as polyuria, polydipsia, nocturia and weight loss can be easily recognized by parents and physicians. This will allow early diagnosis, thus avoiding the potentially life-threatening complications associated with delayed presentation. The lower incidence of T1DM in Brunei Darussalam compared to the rest of the world, may have contributed to the lack of awareness about this medical condition among the general Brunei population. In western countries, where the prevalence of T1DM are higher, prevention programs utilizing education sessions and information dissemination via mass media have been demonstrated to be effective in reducing rates of DKA.[23-25] A mass-media campaign carried out in schools and pediatricians' offices over the course of 8 years in the Italian province of Parma have proven to be successful in reducing the incidence of pediatric DKA from 78% to 12.5%.[23] Public awareness campaigns in the UK have also garnered similar success.[25] In conclusion, the authors suggest conducting public awareness campaigns to help educate the public as well as the healthcare providers in Brunei Darussalam on symptoms associated with childhood T1DM to enable the early diagnosis and prevention of DKA.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CYW: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **AMLY:** Data curation, Writing – review and editing, Supervision; **CFC:** Formal analysis, Data curation, Writing – review and editing, Visualization; **INSS:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – review and editing, Supervision, Project administration.

Author Disclosure
The authors declared no conflict of interest.

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APPENDIX

ICD-10 Codes for Type 1 Diabetes Mellitus available on Bru-HIMS

ICD-10 Codes	Description
E10	Type 1 diabetes mellitus (T1DM)
E10.0	T1DM: With coma
E10.1	T1DM: With ketoacidosis
E10.2	T1DM: With renal complications
E10.3	T1DM: With ophthalmic complications
E10.4	T1DM: With neurological complications
E10.5	T1DM: With peripheral circulatory complications
E10.6	T1DM: With other specified complications
E10.7	T1DM: With multiple complications
E10.8	T1DM: With unspecified complications
E10.9	T1DM: Without complications