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Risk Factors Associated with Cardiac Autonomic Neuropathy in Type 1 Diabetes Mellitus

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ABSTRACT

Background: Cardiac Autonomic Neuropathy (CAN) is one of Type 1 Diabetes Mellitus complications with a high mortality rate. This condition might occur right after T1DM is diagnosed but is often asymptomatic. Cardiac Autonomic Reflex Tests (CART's) are one of the gold standard, non-invasive diagnostic with high sensitivity used for screening but rarely used in children. Some risk factors are associated with CAN, and one of them is poor glycemic Control.
Objective: To delineate risk factors associated with Cardiac Autonomic Neuropathy in children with Type 1 Diabetes Mellitus at Dr. M Jamil Padang Hospital.
Methods: A diagnostic test study was performed on children aged under 18 years old who came to the outpatient pediatric endocrinology clinic of M. Djamil Hospital or Pediatric Ward between February till August 2022 whom caregivers agreed to sign in the informed consent and follow instructions to do one of CART's maneuver called Heart Beat to Deep Breathing with ECG and draw a level HbA1C as Glycemic Control. Secondary data was collected from medical records. Data analysis was performed with a 2x2 table using a computer program
Result: 34 samples were collected, with mean age T1DM 13,14±2,75 years and mean age at onset 10,4±2,65 years. CAN was diagnosed in 13 (38,2%) T1DM subjects and there was no signification between onset at age (p=1,0), duration of illness (p=0,653), and Glycemic control (p=0,132).
Conclusion: No significant correlation was found between risk factors associated with Cardiac Autonomic Neuropathy in Type 1 Diabetes Mellitus.

Keywords: CART's, Cardiac Autonomic Neuropathy, Type 1 Diabetes Mellitus

INTRODUCTION

Diabetic neuropathy is one of the most common complications of diabetes mellitus. Types of neuropathy in patients can be peripheral neuropathy and autonomic neuropathy. Autonomic neuropathy in diabetic patients affects the autonomic nervous system which affects the digestive system, cardiovascular system, and urogenital system. The prevalence of autonomic neuropathy in children varies from 1% to 90% in people with type 1 diabetes mellitus and 20% to 73% in people with type 2 diabetes mellitus. According to the Subcommittee of the Toronto Consensus Panel, cardiac autonomic neuropathy (CAN) is defined as a disorder of the autonomic control of the cardiovascular system and is one of the most common and serious complications associated with diabetes but it is often overlooked.[1,2]

The main reasons for this difference in prevalence are the inconsistent diagnostic criteria and the wide range of characteristics of the study population, such as age range, sex, age of onset of diabetes, and duration of

diabetes. Symptoms that can be found in CAN are almost asymptomatic, the earliest sign of CAN may be a change in heart rate variability, but in advanced conditions, several symptoms that may be found include resting tachycardia, orthostatic hypotension, orthostatic tachycardia, and bradycardia syndrome, autonomic dysfunction exercise tolerance, silent ischemia, and sudden cardiac death. The risk of death increases with the discovery of two or more abnormalities on autonomic tests. Screening in patients with diabetes is very important to predict early symptoms of NOK, one of which is by using Cardiac Autonomic Reflex Tests (CART's).[3,4]

The pathogenesis of CAN itself is unclear, but with the presence of risk factors and the development of CAN, mortality may be avoided by early identification in patients with type 1 diabetes mellitus. Cardiac autonomic neuropathy (CAN) is a disorder that contributes to the morbidity and mortality of patients with diabetes. A meta-analysis study stated in several studies that the mortality rate of patients with type 1 diabetes mellitus with CAN increased significantly from 37% to 53% in a 5-year follow-up. Our aim in this cross-sectional study was to delineate risk factors associated with cardiac autonomic neuropathy in children with Type 1 Diabetes Mellitus at Dr. M Jamil Padang Hospital.[5,6]

MATERIALS & METHODS

This descriptive cross-sectional study design and diagnostic test study were performed on children aged less than 18 years old with T1DM, who came to the outpatient pediatric endocrinology clinic of Dr. M. Djamil Hospital or Pediatric Ward from February to August 2022 whom caregivers agreed to sign in the informed consent and follow instructions to do one of CART's maneuver called Heart Beat to Deep Breathing with ECG and draw a level HbA1C as Glycemic Control. Secondary data was collected from the medical record. The exclusion criteria were those who have a comorbid disease that affects the heartbeat like hyperthyroid, systemic lupus erythematosus, severe anemia, or congenital heart disease which has already been confirmed with echocardiography before. Standard tests were used to diagnose CAN which was devised by Ewing and Clark which was Heart rate variation during deep breathing. The patient was asked to take deep breaths (6 breaths/min) with ECG recording. The longest and shortest R-R intervals were calculated as beats per minute. R-R variation is normal >15 beats/minute, borderline 11-14 beats/min, and diagnostic <10 beats/min. The high-performance liquid chromatography method was used to measure glycosylated hemoglobin (HbA1C). Glycemic control was controlled HbA1C ≤ 7,5 %) and uncontrolled (HbA1C > 7,5%).

STATISTICAL ANALYSIS

Data analysis was performed using the statistical program Social Science Software for Windows (SPSS) version 23.0. Quantitative variables are presented as mean and standard deviation (SD). Qualitative variables are displayed as frequencies and percentages. The relationship between CAN and T1DM age of onset, duration of T1DM, and glycemic control was assessed using the chi-square test. A P-value of 0.5 or less was considered statistically significant.

RESULT

Demographic data of T1DM children is shown in Table 1. Thirty-four with T1DM were included in this study with 20 (58.8%) males and 12(41.2%) females. The patient's age range was 13,14 ±2,76 years.

Table 1. Characteristics of Subjects

Characteristics	f (%)	Mean±SD
Age (years)		13,14 ±2,76
Age of Onset (years)		10.47 ±2,65
Gender		
Male	20(58,8)	

Female	14(41,2)	
Duration T1DM (years)		2,70±2,15
< 5 years	28 (82,4)	
≥ 5 years	6 (17,6)	
Glycemic Control		11,14±3,03
Uncontrolled	29 (85,3)	
Controlled	5 (14,7)	
History of Diabetes Mellitus in Family		
Yes	6 (17,6)	
No	28 (82,4)	
Diabetic Ketoacidosis (DKA) Events		
Yes	27 (79,4)	
No	7 (20,6)	
Cardiac Autonomic Neuropathy		
Positive	13(38,2)	
Negative	21(61,8)	

Table 1. showed the average age at diagnosis of T1DM was 10.47 ± 2.65 years and more than half of the respondents had uncontrolled metabolic control status as many as 29 (85.3%) people with an average of 11.14 ± 3.03%. Most of the respondents had experienced DKA and there were 13 (38.3%) respondents who had cardiac autonomic neuropathy (CAN).

Table 2 Average age of onset of patients diagnosed with T1DM with CAN in children at Dr. M Djamil Hospital Padang

Complication	f (%)	The onset of Age (mean±SD)	p-value
CAN Positive	13(38,2)	10,38±2,53	0.0885
CAN Negative	21(61,8)	10,5±2,7	

Table 3 Relationship between the age of onset of patients diagnosed with DMT1 and the incidence of CAN in children with T1DM at Dr. M Djamil Hospital, Padang

Onset of Age	CAN		Total (f/%)	p-value
	Positive (f/%)	Negative (f/%)		
≥ 10 years old	8 (23,4)	14 (41,3)	22 (64,7)	0,761
< 10 Years old	5 (14,8)	7 (20,5)	12 (35,3)	
Total	13 (38,2)	21 (61,8)	34 (100)	

Based on Table 2, the group of children with CAN was found with an average age of onset of diagnosis of 10.38 ± 2.53 years (p-value> 0.05) but happened to 8 (23,4%) older children diagnosed with diabetes (table 3), although statistically no significant relationship between the age of onset of patients diagnosed with T1DM with CAN.

Table 4 The average duration of patients diagnosed with T1DM and the incidence of CAN in children with T1DM at Dr. M Djamil Hospital, Padang

Complication	f (%)	Duration of disease (mean±SD)	p-value
CAN Positive	13(38,2)	2,69±2,32	0.977
CAN Negative	21(61,8)	2,71±2,1	

Table.5 The relationship between the duration of patients diagnosed with T1DM and the incidence of CAN in children with T1DM at Dr. M Djamil Hospital, Padang

Duration of Disease	CAN		Total (f/%)	p-value
	Positive (f/%)	Negative (f/%)		
≥ 5 years	3 (8,8)	3(8,8)	6(17,6)	0.513
< 5 years	10 (29,4)	18(53)	28(82,4)	
Total	13(38,2)	21(61,8)	34	

Table 4 showed that CAN occurred with an average duration of diagnosis of 2.69 ± 2.32 years compared with children without NOK with an average duration of diagnosis of 2.71 ± 2.1 years (p-value> 0.05). Related the majority of children with CAN have a duration of T1DM of less than 5 years (table 5).

Table.6 Average HbA1C levels with the incidence of CAN in children with T1DM at Dr. M Djamil Hospital Padang

Complication	f (%)	*HbA1C* (mean±SD)	p-value
CAN Positive	13(38,2)	12,05 ±2,75	0,174
CAN Negative	21(61,8)	10.5±3,13	

Table.7 Relationship of metabolic control (HbA1C) with the incidence of CAN in children with T1DM at Dr. M Djamil Hospital Padang

Glycemic Control	CAN		Total (f/%)	p-value
	Positive (f/%)	Negative (f/%)		
Uncontrolled	13 (38,2)	16 (47,1)	29(85,3)	0,057
Controlled	0 (0)	5(14,7)	5(14,7)	
Total	13 (38,2)	21 (61,8)	34	

Table 7 showed 13(38,2) children with CAN have uncontrolled glycemic status with an average HbA1C level of 12.05 ± 2.75% (p-value> 0.05) so there was no statistical relationship between HbA1C levels and the incidence of CAN in children with T1DM.

DISCUSSION

Patient demographic characteristics include age, sex, age of onset at diagnosis, length of time diagnosed with DMT1, family history of diabetes mellitus, history of ketoacidosis, and metabolic control status (HbA1C). In this study, the patient's current age range was 13.14 ± 2.76 years, and the patient's age range when he was first diagnosed with DMT1 was 10.4 ± 2.65 years. The majority of respondents were male (58.8%) and almost all respondents had experienced diabetic ketoacidosis (79.4%).

The latest data from The International Diabetes Foundation (IDF) shows that around 1.2 million children and adolescents range 0-19 years worldwide suffer from Diabetes, especially T1DM with an incidence of 145.000 new cases per year and the highest number of cases until 2021 was 295.000 cases in the European region.[7] Until 2019, 1249 children with T1DM were recorded in Indonesia with an estimated seven-fold increase in the incidence of T1DM in children and adolescents from 3.88 to 28.19 per 100 million in 10 years with the proportion of females with T1DM (60%) higher than males (28.6%).[8] A systematic review study by Lopera et al, found cases with the lowest age group up to the age of fewer than 5 years, with an increased incidence in the 5-10 year age group, but compared to the previous 2 training periods, the incidence increased in the 0-4 year age group (1.9x) compared to other age groups.[9]

The average HbA1C level in the study was 11.14 ± 3.03% with the lowest level being 6% and the highest level being 16.8% with uncontrolled metabolic status in 76.5% of cases. In a study conducted by Djonou et al.[10] in a cross-sectional study in Africa in 2019, an average HbA1C level of 9.2 ± 2.5% (67% of cases) was obtained, while a retrospective study conducted by Zahrani et al in Saudi Arabia obtained an average HbA1C level of 9.6 ± 1.93% with no significant difference between types gender.[11] Similar results were found in a retrospective study by Dumrisilp et al in Thailand which also found 78% of respondents (9.9±1.6%) had poor glycemic control.[12]

Because autonomic neuropathy can affect one-of-a-kind organs inside the body, its signs and symptoms can vary. Cardiac autonomic neuropathy progresses slowly over time and carries a high risk of mortality and morbidity. The prevalence of CAN varies widely between various studies. This study has shown that CAN is a common complication affecting approximately 38.2% of subjects with T1DM.

In this study, the results obtained were 5 respondents (14.7%) who had CAN with a diagnosed age of T1DM less than 10 years old and 8 respondents (23.5%) with a diagnosed age of DMT1 more than equal 10 years old, with an average age of diagnosed DMT1 10.38 ± 2.53 years old, but no significant relationship was found (p>0.05). This is inconsistent with several studies

regarding the incidence of CAN. Stella et al's study, with patient data taken from the Epidemiology of Diabetes Complication Study (EDC), complications of CAN occurred in 104 of 373 subjects with T1DM with an older age of onset and longer duration of illness.[13] In the cohort study by Foster et al, an increase in HbA1C levels was observed for 3 years and was dominated by the adolescent age group.[14] This may be related to the status of puberty when a patient is diagnosed with DMT1 which plays a role in adequate glycemic control, where puberty-related insulin resistance occurs which results in changes in synthesis and hormones in the body which will change insulin sensitivity. One of the hormones that are influenced by the Growth Hormone which works opposite to the function of insulin in glucose metabolism (GH-IGF1 Axis) which will increase the ketogenesis process. Svensson et al study stated that the incidence of disease complications increased before puberty compared to after puberty, where cardiovascular complications were more dominant in patients with diabetes during puberty.[15]

In this study, none of the studied children had clinical manifestations of CAN, and the results obtained were that compared to children without CAN, children with CAN had uncontrolled glycemic control, but had a shorter duration of diabetes (less than 5 years). A systematic review study in Denmark by Rassmusen et al described the incidence of neuropathy T1DM in adolescents from 27 studies varying from 12 to 75%.[16] Differences Prevalence in various studies is assumed to be due to differences in diagnostic criteria where not all examinations are carried out with the cut-off variant, as well as exposure to other risk factors that are thought to influence the incidence of complications in each individual, but it can be concluded in this study that the early stage of CAN is completely asymptomatic. Another study by Foster et al showed the minimum duration incidence of CAN is 3 years after being diagnosed with T1DM.[14] While the cohort study by Sauder et al explained that there was more than one complication that occurred in the very high-risk group (having high HbA1C levels) with a duration of suffering from T1DM for an average of 7.8 years.[17]

Most of the studies state that the longer it is diagnosed, the more likely complications will occur. This is also in accordance with the study by Stella et al and another study by Gomes et al that longer duration increased incidents of CAN statistically significant. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening for peripheral neuropathy starting at the age of 11 years with a range of 2-5 years since DMT1 was diagnosed, and carried out periodically.[18]

Similarly in our study, In the 2018 SEARCH Cohort Study by Jaiswal et al, obtained the result when CAN happened mostly in a shorter duration (less than 5 years). This may be due to the involvement of other risk factors such as glycemic levels (HbA1C), levels of lipid profile, nutritional status, and type of anti-diabetic medication consumed so that the length of time diagnosed is not the sole factor influencing the incidence of CAN.[19,20]

Hyperglycemia causes oxidative stress and toxic glycosylation products that cause changes in mitochondrial function, membrane permeability, and endothelial function. Neuropathy affects the longest nerve fibers first, so the initial manifestation of CAN is related to damage to the vagus nerve which is responsible for 75% of parasympathetic activity. Glycemic control (HbA1C) is a marker that describes the condition of glycemic control only in the last 3 months, and it is difficult to assess glycemic control in the past and causes variations in the significance of the glycemic control relationship to the incidence of CAN in cross-sectional studies where data collection only obtained control in the last 3 months, although in terms of findings, the incidence of CAN has a fairly high percentage (30%).[21,22]

Cardiac autonomic neuropathy (CAN) is a chronic complication of T1DM that is associated with a risk of cardiac mortality and morbidity. Several studies in T1DM patients have shown that poor glycemic control and long duration of diabetes are associated with an increased incidence. The role of hyperglycemia in the development and progression of NOK itself has good and significant records with strong evidence based on the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complication (DCCT/EDIC) study where intensive insulin treatment with a target of near-normal blood sugar reduces the incidence of CAN was up to 53% compared to the conventionally managed group and remained with a lower prevalence and reduced incidence of NOK by 31% after 14 years of follow-up.[23]

To summarize, in this study CAN is present during the early stages of T1DM children and adolescents. Strict glycemic control is essential to halt the onset of CAN, improving disease outcomes and quality of life. Public awareness campaigns might help in better management of T1DM.

CONCLUSION

All of the child respondents with T1DM were more than half male, most of the respondents had been known to have suffered from T1DM for a long time with an average of fewer than five years. More than half of the respondents had uncontrolled metabolic control status with most of the respondents having experienced diabetic ketoacidosis and had no family history of DM. The overall prevalence of cardiac autonomic neuropathy among diabetic patients was found to be as 38.2 %. The outcome of our study documents the high prevalence of CAN in type 1 diabetic children and adolescents during the early stage of the disease. Intense diabetic control is essential for better patient outcomes. We recommend routine evaluation for CAN in T1DM, especially over five years duration of the disease.

Declaration by Authors

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