Impaired Awareness of Hypoglycemia in a Population-Based Sample of Children and Adolescents With Type 1 Diabetes

TRANG T. LY, MBBS[1]
PATRICIA H. GALLEGO, MD, MSC[1]
ELIZABETH A. DAVIS, FRACP[1,2]
TIMOTHY W. JONES, FRACP, MD[1,2]

OBJECTIVE — To determine the prevalence and clinical associations of impaired awareness of hypoglycemia in a population-based sample of children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A validated questionnaire was administered to 656 patients with type 1 diabetes over a 6-month period to determine hypoglycemia awareness status. Case ascertainment was 79% of the clinic population. The rate of severe hypoglycemia was determined by data collected prospectively in the preceding year.

RESULTS — Impaired awareness of hypoglycemia was present in 29% of patients. Patients with impaired awareness of hypoglycemia had an earlier onset of diabetes ($P < 0.001$), were younger ($P < 0.001$), and had lower mean levels of A1C since diabetes onset ($P = 0.006$) and at their last visit ($P = 0.001$). The overall rate of severe hypoglycemia was 24.5 episodes per 100 patient-years in the preceding year. The severe hypoglycemia rate was higher in those with impaired awareness of hypoglycemia (37.1 vs. 19.3 episodes per 100 patient-years, $P < 0.001$). Among patients aged <6 years ($n = 46$), 59% of care providers reported impaired awareness of hypoglycemia, and the rate of severe hypoglycemia was significantly higher in those reporting impaired awareness (33.3 vs. 52 episodes per 100 patient-years, $P = 0.02$). More patients with recurrent hypoglycemia reported impaired awareness of hypoglycemia (47 vs. 28%, $P = 0.03$).

CONCLUSIONS — A significant proportion of children and adolescents with type 1 diabetes have impaired awareness of hypoglycemia. Screening for impaired awareness is an important component of routine diabetes care and can identify patients at increased risk of a severe hypoglycemic event.

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Hypoglycemia is a well-known complication of insulin therapy in children and adolescents with diabetes. The risk of recurrent and severe hypoglycemia causes significant anxiety and emotional morbidity for patients and their families and is a limiting factor in the achievement of tight glycemic control.

Hypoglycemia unawareness is defined as the onset of neuroglycopenia before autonomic activation (1). Patients have defective symptomatic and counterregulatory hormone responses to hypoglycemia and are unable to initiate self-treatment. This impaired awareness has been associated with severe hypoglycemia, accounting for 36% of the hypoglycemia that occurred while subjects were awake during the Diabetes Control and Complications Trial (2).

The neurological consequences of severe hypoglycemia are particularly important in the young child with type 1 diabetes. Hypoglycemia has been associated with a decrease in neurocognitive function in children with type 1 diabetes, particularly those in whom diabetes is diagnosed before the age of 5–6 years (3–5). Repeated hypoglycemic seizures in young children may also cause structural brain changes, as suggested by the prevalence of mesial temporal sclerosis in 16% of a cohort of children with early-onset type 1 diabetes (6). Severe hypoglycemia adds to the considerable burden of disease in families through increased anxiety, poor sleep, increased hospitalizations, excessive lowering of insulin dose, and worsening of glycemic control (7).

For clinical and research purposes, determining the presence of hypoglycemia unawareness in children and adolescents with diabetes is important. Various methods have been applied, including the use of self-reporting symptom questionnaires and inducing experimental hypoglycemia in the laboratory to determine the symptom response threshold and counterregulatory hormone response. The aim of this study was to determine the prevalence of impaired awareness of hypoglycemia in a large, population-based cohort with childhood-onset type 1 diabetes, assessed with a self-reporting questionnaire, and to study the relationship between impaired hypoglycemia awareness and severe hypoglycemia.

RESEARCH DESIGN AND METHODS

— Children and adolescents with type 1 diabetes aged between 6 months and 19 years and diabetes duration of at least 6 months, attending pediatric diabetes clinics at Princess Margaret Hospital were eligible to participate in the study. Princess Margaret Hospital is the only pediatric diabetes referral center for the population of Western Australia, and almost all children with type 1 diabetes in the state are registered and treated here. Previous studies have shown that this center has a case ascertainment close to 100% (8,9). All patients have had ongoing prospective documentation from diagnosis, at 3-month intervals, of hypoglycemic events, diabetic ketoacidosis, and glycemic control measured by A1C.

Patients and care providers had undergone extensive diabetes education during their initial inpatient admission at diagnosis, including the recognition and treatment of hypoglycemic episodes. All patients were given glucagon at discharge, and care providers had been instructed on

From the [1]Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children, Perth, Western Australia, Australia; and the [2]Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Western Australia, Australia.
Corresponding author: Timothy W. Jones, tim.jones@health.wa.gov.au.
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its use. Insulin regimens included a combination of twice-daily injections (NPH insulin and analog) through to four injections per day with analog insulins and continuous subcutaneous insulin infusion therapy.

A validated questionnaire to characterize hypoglycemia unawareness was applied to children and adolescents and/or their care providers. This questionnaire was based on a tool used to assess reduced awareness of hypoglycemia in an adult population by Clarke et al. (10). This questionnaire has been shown to accurately identify patients with impaired awareness of hypoglycemia for both clinical and research purposes (11). In this study, patients scoring ≤3 were categorized as having normal awareness and patients scoring ≥4 were categorized as having impaired awareness. The original items for scoring severe hypoglycemia in the previous 12 months and moderate hypoglycemia in the previous 6 months were not included in our questionnaire as these data were collected prospectively in this clinic population.

For children up to the age of 10 years or those who were unable to fill out the questionnaire, parents or care providers were asked to complete it. For children aged between 10 and 12 years, both care providers and children completed the questionnaire. Children aged >12 years completed the questionnaires independently. The test-retest reliability of this questionnaire was verified by retesting the first 100 patients and/or care providers.

Definition of severe hypoglycemia

For the purposes of this study, severe hypoglycemia was defined as an event leading to loss of consciousness or seizure. This strict definition was used because it is an unequivocal end point rather than the more commonly used definition of severe hypoglycemia, which is an event requiring help from another individual. This more common definition is difficult to apply to young children, particularly those <6 years of age, because all hypoglycemic episodes may require assistance in this age-group. Patient data were collected prospectively at routine clinic visits every 3 months using a specifically designed data collection form, completed by a limited number of physicians. The details of data collection have been documented previously (9,12). In summary, both patients and parents were instructed on how to record details of the hypoglycemic event including blood glucose levels and response to treatment. All care providers were instructed to obtain a blood glucose value at each event once the safety of the child was assured. In our cohort, glucose values were obtained >98% of the time. This information was subsequently reviewed by the clinician and, if validated, was recorded on the data collection form. The physician reviewed the history of the event, the glucose recording and its timing, and the recovery history before judging the event to be hypoglycemia related. In addition to the logbooks, most families phoned the diabetes management team to receive advice on event management after a hypoglycemic event of this severity. These calls were recorded. We note that there was a close correlation between recall at the clinic through logbooks and calls to the diabetes team, providing further evidence that recall was accurate over this time period.

Definition of recurrent hypoglycemia

Recurrent hypoglycemia was defined as the occurrence of ≥2 episodes of severe hypoglycemia in the preceding year.

Laboratory measurements

A1C was measured at each 3-month visit. A1C was assessed by an agglutination inhibition immunoassay (Ames DCA 2000; Bayer, Mishawaka, IN). The inter- and intra-assay coefficients of variation were 2.5 and 2.3%, respectively.

Statistical analysis

Clinical characteristics of the study groups were compared using Student's *t* test (mean ± SD) for variables normally distributed and the Mann-Whitney *U* test (median ± SD [interquartile range]) for those with a nonnormal distribution.

RESULTS

— A total of 656 patients and/or care providers (317 male and 339 female) completed the questionnaire over a 6-month period. During this period, there were 829 patients attending the clinic, giving a case ascertainment of 79%. Mean ± SD age was 12.8 ± 4.0 years with A1C of 8.5 ± 1.0% since diagnosis and 8.1 ± 1.4% at the last visit. During the 12 months before the questionnaire visit, data were collected at each 3-month visit. The patients had to have had at least three visits in the preceding 12 months to be included. Of all subjects, the mean number of visits was 3.7 in the previous year, and 92% of patients had 4 visits recorded.

The clinical characteristics of the cohort with impaired and normal awareness are shown in Table 1. Impaired awareness of hypoglycemia was present in 29% of patients. No differences were observed in sex or diabetes duration; however, patients with impaired hypoglycemia awareness had an earlier onset of diabetes ($P < 0.001$), were younger ($P < 0.001$), and had lower levels of mean A1C since diabetes onset and at their last visit ($P = 0.006$ and $P = 0.001$, respectively). Among patients aged <6 years ($n = 46$), 19 patients (41%) and 27 patients (59%) were observed in the group with impaired and normal awareness, respectively ($P < 0.001$). There was no difference observed in hypoglycemia awareness scores between patients receiving injections compared with those receiving continuous subcutaneous insulin infusion therapy.

In the preceding year, a total of 161 episodes of severe hypoglycemia were recorded among all patients, giving an overall incidence of 24.5 episodes/100 patient-years. This rate was significantly higher among patients reporting impaired hypoglycemia awareness (37.1 vs. 19.3 episodes per 100 patient-years, $P < 0.001$). Among patients aged <6 years, the rate of severe hypoglycemia was significantly higher in those with reported impaired awareness (33.3 vs. 52 episodes per 100 patient-years, $P = 0.02$).

Table 2 summarizes the clinical features of patients with recurrent and nonrecurrent hypoglycemia in the preceding year. Thirty-eight patients had recurrent hypoglycemia with no differences in sex, age of onset, diabetes duration, or A1C between the recurrent and nonrecurrent groups. More patients with recurrent hypoglycemia reported impaired awareness of hypoglycemia (47% vs. 28%, $P = 0.03$). As expected, the rate of severe hypoglycemia was much higher in the recurrent group (252.6 vs. 10.5 episodes per 100 patient-years).

Table 3 demonstrates the findings in patients with diabetes duration >5 years compared with those with diabetes duration <5 years. In the group with diabetes for >5 years, higher levels of mean A1C since diabetes onset were observed ($P < 0.001$). Even with this higher A1C, a higher rate of severe hypoglycemia (32.6 vs. 17.8 episodes per 100 patient years, $P < 0.001$) occurred among those with a diabetes duration of >5 years; however,

Table 1—*Characteristics of children and adolescents with type 1 diabetes with normal and impaired hypoglycemia awareness*

	Total	Normal awareness	Impaired awareness	*P*
n (%)	656	465 (71)	191 (29)	
Sex (male/female)	317/339	221/244	96/95	NS
Age at diagnosis (years)	7.4 ± 4.0	8.0 ± 4.0	5.9 ± 3.8	<0.001
Age at questionnaire (years)	12.8 ± 4.0	13.5 ± 3.6	11.0 ± 4.4	<0.001
Duration of diabetes (years)	5.4 ± 3.9	5.5 ± 3.9	5.2 ± 3.8	NS
A1C (%) since diagnosis	8.5 ± 1.0	8.6 ± 1.0	8.3 ± 1.0	0.006
A1C (%) at last visit	8.1 ± 1.4	8.2 ± 1.4	7.8 ± 1.2	0.001
Severe hypoglycemia: episodes in preceding year	161	90	71	
Rate of severe hypoglycemia (episodes/100 patient-years)	24.5	19.3	37.1	<0.001
Patients, age ≤6 years, *n* = 46 (%)	46	41	59	<0.001
Rate of severe hypoglycemia in patients aged ≤6 years (episodes/100 patient-years)	21.7	5.2	33.3	0.02

Data are means ± SD unless indicated otherwise.

no differences in hypoglycemia awareness were observed between the groups.

CONCLUSIONS — In this study, impaired hypoglycemia awareness assessed by a validated, self-reporting questionnaire was reported in 29% of children and adolescents. Overall, the rate of severe hypoglycemia was almost double in the group with impaired awareness. This was even more prominent in children aged <6 years with a 6-fold increase in the rate of severe hypoglycemia in the group with impaired awareness, as observed by care providers. Care providers of children in this age-group have difficulty recognizing hypoglycemia in their children. This group of care providers reported a change in the pattern of symptoms associated with hypoglycemia in their children. These results suggest that in children as well as adults, screening for impaired awareness of hypoglycemia is an important component of routine diabetes care and can help identify patients at increased risk of having a severe hypoglycemic event.

Our rates of impaired awareness of hypoglycemia are consistent with those in a previous study reported by Barkai et al. (13). In this prospective study of 130 children and adolescents with type 1 diabetes, impaired awareness was reported by 37% of patients. Patients with impaired awareness had a much greater frequency of hypoglycemia-related coma or seizure (14.6 vs. 1.2 episodes per 100 patient-years), and their overall incidence of hypoglycemia-related coma or seizure was 6.2 per 100 patient-years (13). Clearly, despite changes in insulin therapy in the last decade, hypoglycemia unawareness remains common.

Our results are also consistent with several recent studies in adults with type 1 diabetes. The prevalence of impaired awareness is similar to that in adults despite a shorter duration of diabetes in children. There are also differences in treatment regimens and counterregulatory hormone and symptom responses to hypoglycemia (14–16). Geddes et al. (17) reported the prevalence of impaired awareness of hypoglycemia in ~20% of a large, unselected adult population with type 1 diabetes. These patients also had a 6-fold increase in the frequency of severe hypoglycemia in the preceding year. Similar rates of prevalence of impaired awareness and the association with severe hypoglycemia in adults have been reported by others (18).

Hypoglycemia unawareness has been extensively studied in adult patients. In both adults and adolescents, it is associated with defective counterregulatory hormone response, also known as hypoglycemia-associated autonomic failure (19). In this present study, we found that more children with recurrent hypoglycemia reported impaired awareness of hypoglycemia. This finding is not surprising given that even short, prior exposure to hypoglycemia can reduce the magnitude of epinephrine and other counterregulatory hormone responses as well as the autonomic symptom responses to a subsequent hypoglycemic episode (20). This shifts the glycemic threshold for these responses to a lower level of plasma glucose, which further increases the risk of subsequent severe hypoglycemic episodes. Hypoglycemia is more frequent in the young (21), which may explain the higher frequency of impaired awareness in children and adolescents. In adults, hypoglycemia unawareness is often associated with older age and longer duration of diabetes

Table 2—*Characteristics of children and adolescents with type 1 diabetes with recurrent and nonrecurrent hypoglycemia in the previous year*

	Recurrent hypoglycemia	Nonrecurrent hypoglycemia	*P*
n (%)	38 (6)	618 (94)	
Sex (male/female)	26/12	291/327	NS
Age at diagnosis (years)	6.6 ± 3.6	7.4 ± 4.1	NS
Age at questionnaire (years)	12.8 ± 4.1	12.8 ± 4.0	NS
Duration of diabetes (years)	6.2 ± 3.6	5.4 ± 3.9	NS
A1C (%) since diagnosis	8.5 ± 0.9	8.5 ± 1.0	NS
Severe hypoglycemia: episodes in preceding year	96	65	
Rate of severe hypoglycemia (episodes/100 patient-years)	252.6	10.5	<0.01
Impaired awareness of hypoglycemia (%)	47	28	0.031

Data are means ± SD unless indicated otherwise.

Table 3—*Characteristics of children and adolescents with duration of diabetes of >5 and <5 years*

	Duration <5 years	Duration >5 years	*P*
n (%)	359/656 (55)	297/656 (45)	
Sex (male/female)	182/177	135/162	NS
Age at diagnosis (years)	9.1 ± 4.2	5.4 ± 3.1	<0.001
Age at questionnaire (years)	11.7 ± 4.2	15.0 ± 3.0	<0.001
Duration of diabetes (years)	2.5 ± 1.4	8.4 ± 2.9	<0.001
A1C (%) since diagnosis	8.20 ± 1.0	8.8 ± 1.0	<0.001
Severe hypoglycemia: episodes in preceding year	64	97	
Rate of severe hypoglycemia (episodes/100 patient-years)	17.8	32.6	<0.001
Impaired awareness of hypoglycemia (%)	31	27	NS

Results expressed in mean ± SD unless otherwise indicated.

(17,22). In our study, however, patients with a duration of diabetes >5 years did not have higher rates of impaired hypoglycemia awareness compared with patients with a duration of <5 years.

Impaired hypoglycemia awareness is clearly a significant problem for children and adolescents with type 1 diabetes, and these children have a greater risk of having a hypoglycemia-related coma or seizure. This risk adds to the considerable burden of disease for families. There is evidence, however, that in adults with hypoglycemia unawareness, this phenomenon can be reversed by meticulously avoiding hypoglycemia for 2–3 weeks (23,24), although this is difficult to accomplish in young children. It is likely that the pathophysiology of the genesis of hypoglycemia unawareness and its associated counterregulatory hormone deficit is similar in the young to that in adults because attempts to restore responses by strictly avoiding hypoglycemia, at least in preliminary studies, appear to be successful (25).

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