Contents available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Detection of hypoglycemia associated EEG changes during sleep in type 1 diabetes mellitus

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ARTICLE INFO

Article history:
Received 19 December 2011
Received in revised form
30 March 2012
Accepted 23 April 2012
Published on line 17 July 2012

Keywords:
Type 1 diabetes
Hypoglycemia
Alarm
Real-time EEG
Unawareness

ABSTRACT

Objective: Nocturnal hypoglycemia is a feared complication to insulin treated diabetes. Impaired awareness of hypoglycemia (IAH) increases the risk of severe hypoglycemia. EEG changes are demonstrated during daytime hypoglycemia. In this explorative study, we test the hypothesis that specific hypoglycemia-associated EEG-changes occur during sleep and are detectable in time for the patient to take action.

Research design and methods: Ten patients with type 1 diabetes (duration 23.7 years) with IAH were exposed to insulin-induced hypoglycemia during the daytime and during sleep. EEG was recorded and analyzed real-time by an automated multi-parameter algorithm. Participants received an auditory alarm when EEG changes met a predefined threshold, and were instructed to consume a meal.

Results: Seven out of eight participants developed hypoglycemia-associated EEG changes during daytime. During sleep, nine out of ten developed EEG changes (mean BG 2.0 mmol/l). Eight were awakened by the alarm. Four corrected hypoglycemia (mean BG 2.2 mmol/l), while four (mean BG 1.9 mmol/l) received glucose infusion. Two had false alarms. EEG-changes occurred irrespective of sleep stage. Post hoc improvement indicates the possibility of earlier detection of hypoglycemia.

Conclusions: Continuous EEG monitoring and automated real-time analysis may constitute a novel technique for a hypoglycemia alarm in patients with IAH.

1. Introduction

Hypoglycemia is a feared complication to insulin-treated Type 1 Diabetes (T1D) and is often the limiting factor for further intensification of treatment [1]. Patients with T1D have severe hypoglycemic events 1–3.2 times per year [2–4], defined as being cognitively impaired to such an extent that they need help from others to restore euglycaemia [3]. The rate increases

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0168-8227/$ – see front matter
http://dx.doi.org/10.1016/j.diabres.2012.04.014

with increasing duration of diabetes [3] and intensified treatment [5].

Impaired awareness of hypoglycemia (IAH) is defined as a reduced or abolished ability to sense and respond to hypoglycemia, and is a predictor for risk of severe hypoglycemia [2,6]. Hypoglycemia awareness decreases with the increased duration of diabetes, tight glycemic control and recent hypoglycemic episodes [7,8]. Furthermore, hormonal counter-regulation diminishes with increased duration of diabetes [1].

The fear of hypoglycemia may prevent the patient from obtaining tight glucose control [1] which is correlated with decreased risk of mortality, cardiovascular morbidity and micro vascular disease [1,8]. A hypoglycemia alarm system might allow tighter glycemic control without increasing the risk and fear of hypoglycemia.

The characteristic properties of the electroencephalogram (EEG) during hypoglycemia include higher amplitude and lower frequency and are distinct from the normal EEG during euglycaemia [9]. About 50% of all hypoglycemic events occur during sleep at night [8]. Sleep EEG differs from that in the awake state by occurrence of slow wave patterns thus sharing some of the properties seen during hypoglycemia.

It has previously been shown that hypoglycemia-associated EEG-changes occur approximately 30 min prior to severe cognitive impairment (range 3–113 min) in the awake patient with T1D. Furthermore these changes which were recorded from a single subcutaneous electrode during daytime could be detected by an automated mathematical algorithm [10]. The hypoglycemia associated changes in the EEG have also been identified in children [11].

The aim of this study is to investigate if a real-time, computerized EEG-analyzing algorithm can detect hypoglycemia-associated EEG changes irrespective of sleep stage and, if so, might be used as an alarm system for hypoglycemia during sleep and in the awake state. Furthermore, we tested whether the alarm system can detect impending hypoglycemia in due time for the patient to take action. Since patients with IAH are the target group for a hypoglycemia device, we tested this specific group of T1D patients in the study.

2. Method and material

Ten patients with T1D were enrolled from the outpatient clinic at the Department of Endocrinology, Sydvestjysk Sygehus, Esbjerg. All participants had IAH as defined by either Gold's method [6] or a history of $\geq$2 severe hypoglycemic events during the last 2 years. Patients with a history of cardiovascular disease (e.g. stroke, acute myocardial infarction, limb ischemia or heart failure), epileptic seizures, structural brain damage (verified through patient charts and radiology reports), use of antiepileptic drugs or beta-blocking agents for any purposes were excluded. For each participant, the study included three visits at least 7 days apart (mean 13 days (range 7–47)). The study was approved by the local ethics committee and followed the Helsinki declaration.

Visit 1 (daytime assessment): the participants arrived in the research unit between 8 and 10 a.m. in a non-fasting state. If blood glucose (BG) was $\leq$4.0 mmol/l on arrival, the participants consumed 100 ml of fruit juice. Under sterile conditions and local analgesia an electrode (Foramen Electrode AD-Tech Medical (WI, USA), length 300 mm, diameter 1.1 mm with 3 contact points with a center-to-center distance of 30 mm) was inserted subcutaneously over the temporal region behind the ear. The electrode was connected to an EEG recorder (g-USBamp, G-TEC, Austria). The EEG was sampled at 512 Hz and analyzed real-time by an automated algorithm (see 'EEG-analysis' below). Prior to inducing hypoglycemia, the alarm-sound, a loud beeping noise, was demonstrated for the patient, and a juice and sandwich were placed on the bed table. Hypoglycemia was induced by infusion of 50 IU of Actrapid® (Novo Nordisk, Bagsværd, Denmark) added to 489.5 ml of 9% saline solution (Baxter NaCl isotonic) and 10 ml of the participants whole blood. The initial infusion rate depended on the BG at the start of the experiment and the infusion rate was subsequently adjusted to achieve a steady fall in plasma glucose of 1.0 mmol/l per 15 min. Venous plasma glucose was measured every 5 min by ABL-705 (Radiometer Denmark, Brønshøj, Denmark). If the participants did not respond to the hypoglycemia alarm by food ingestion, they were given intravenous glucose 20% (Baxter 200 g/l glucose) via peripheral vein catheter (initial infusion rate of 64–103 ml/min). Causes for terminating the induction of hypoglycemia were defined as one of the following: (i) alarm due to EEG changes corrected by the patient by food ingestion, (ii) the patient did not respond to the alarm within 5 min, (iii) BG level was lower than 1.5 mmol/l by two consecutive measurements, or (iv) the patient or investigator requested the experiment to stop (due to severe hypoglycemic symptoms, fear of seizures or other acute complications). At BG 6.0 mmol/l, 3.0 mmol/l, and when the experiment ended, additional blood samples were drawn for the analysis of counter-regulatory hormones. Visit 1 was performed while the patients were awake.

Visit 2 (night assessment with alarm): the patients were encouraged to stay up until late the evening before the study night and only sleep 4–5 h to ensure that they could sleep during the study night. The patients met at the hospital between 9 and 11 p.m. The study procedures were identical to those of visit 1 with the following exceptions: the participants were placed in a bed in a separate room with a dim light to allow the investigator to observe the patient. In addition to the subcutaneous electrode, a full 10/20 electrode montage and electrodes for electromyography, electrooculography and electrocardiography were placed. Induction of hypoglycemia started when the patients had shown clinical signs of sleep for at least 1 h. Causes for termination of hypoglycemia were identical to the daytime assessment and, if necessary, glucose was infused until the patient recovered from symptoms of hypoglycemia. Afterwards, the patient was allowed to sleep until the next morning.

Visit 3 (night assessment without alarm): the purpose of this visit was to ensure that all the participants experienced hypoglycemia. The study procedures were identical to those of visit 2 with one exception: the patient did not receive an alarm when the hypoglycemia-induced EEG-changes exceeded the threshold value. The causes of termination were the same as for the daytime assessment, except for the alarm.

EEG analysis: the development of the algorithm for automated quantitative EEG analysis has previously been