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CASE REPORT

Corneal Confocal Microscopy Identifies Structural Small Fibre Abnormalities in an Adolescent with Type 1 Diabetes and Impaired Awareness of Hypoglycaemia

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Abstract

Impaired awareness of hypoglycaemia (IAH) is present in around 25-40% of individuals with type 1 diabetes mellitus (T1DM). Herein, we present a case of an adolescent with T1DM and IAH who had worse corneal nerve parameters compared to a T1DM adolescent without IAH. Small fibre abnormalities detected by corneal confocal microscopy in an objective easy-to-perform non-invasive test might be a surrogate indicator of underlying autonomic dysfunction in T1DM and IAH.

Key words: corneal confocal microscopy, small fibre, autonomic neuropathy, hypoglycaemia, T1DM

CASE

A 16-year-old adolescent Indian male with type-1 diabetes (T1DM), diagnosed 11 years ago, presented with a one-month history of intermittent episodes of confusion with documented hypoglycaemia. He was on a basal-bolus insulin regimen requiring 26 units/day. His Clarke score was 4, suggestive of impaired awareness of hypoglycaemia (IAH). He had mild tingling and numbness of the extremities with normal monofilament and vibration perception thresholds, suggestive of minimal evidence of clinical neuropathy (Toronto clinical neuropathy score [TCNS]=2). Warm detection thresholds were mildly abnormal. He had no retinopathy. His resting pulse rate was 104 beats/min. Laboratory parameters were: HbA1c 9.3% (78 mmol/mol), creatinine 1.0 mg/dl, urine albumin-creatinine ratio 124 μg/g creatinine. *In vivo* corneal confocal microscopy (CCM) was performed on the patient, an age-matched T1DM child without IAH (TCNS=1, HbA1c 9%, T1DM duration 10 years), and a healthy control to explore the underlying pathophysiological defects. The following parameters were used in the assessment of corneal nerve pathology: (i) corneal nerve fibre density (CNFD), (ii) corneal nerve fibre length (CNFL), (iii) corneal nerve branch density (CNBD).[1]

Figure 1 essentially indicates the presence of poor small nerve fibre morphology i.e., reduced CNFD, CNBD and CNFL in a T1DM child without IAH compared to an age-matched healthy control. When compared to the T1DM child without IAH, the images of our patient with IAH reveals poorer corneal nerve parameters, in particular reduced CNBD and CNFL.

DISCUSSION

Approximately 25–40% of individuals with T1DM have IAH, the hallmark of which is the attenuation of counter-regulatory sympathetic symptoms such as tremors, palpitations, and anxiety, and impaired neuro-hormonal response to hypoglycaemia.[2] Autonomic dysfunction, which includes cardiovascular autonomic neuropathy (CAN), contributes directly to IAH.[2] Cardiovascular reflex tests are considered the gold-standard method for confirming CAN. However, these battery of tests are often difficult to perform in routine clinical practice.[3] Abnormalities in the CCM parameters in diabetes have previously been shown to precede clinical neuropathic deficits and neurophysiological abnormalities of large fibres.[4,5] CCM can objectively detect early corneal nerve fibre damage in T1DM children even in the absence of clinical neuropathy, retinopathy or microalbuminuria.[6] CCM has also been proven to be useful in the assessment of CAN in T1DM.[7] However, the potential role of CCM in an individual with T1DM and IAH has not yet been previously explored. Postganglionic autonomic nerve fibres in both sympathetic and parasympathetic nervous system are unmyelinated small fibres, as are C-sensory fibres that are present in corneal sub-basal plexus. Herein, we demonstrate that the changes in CCM in a patient

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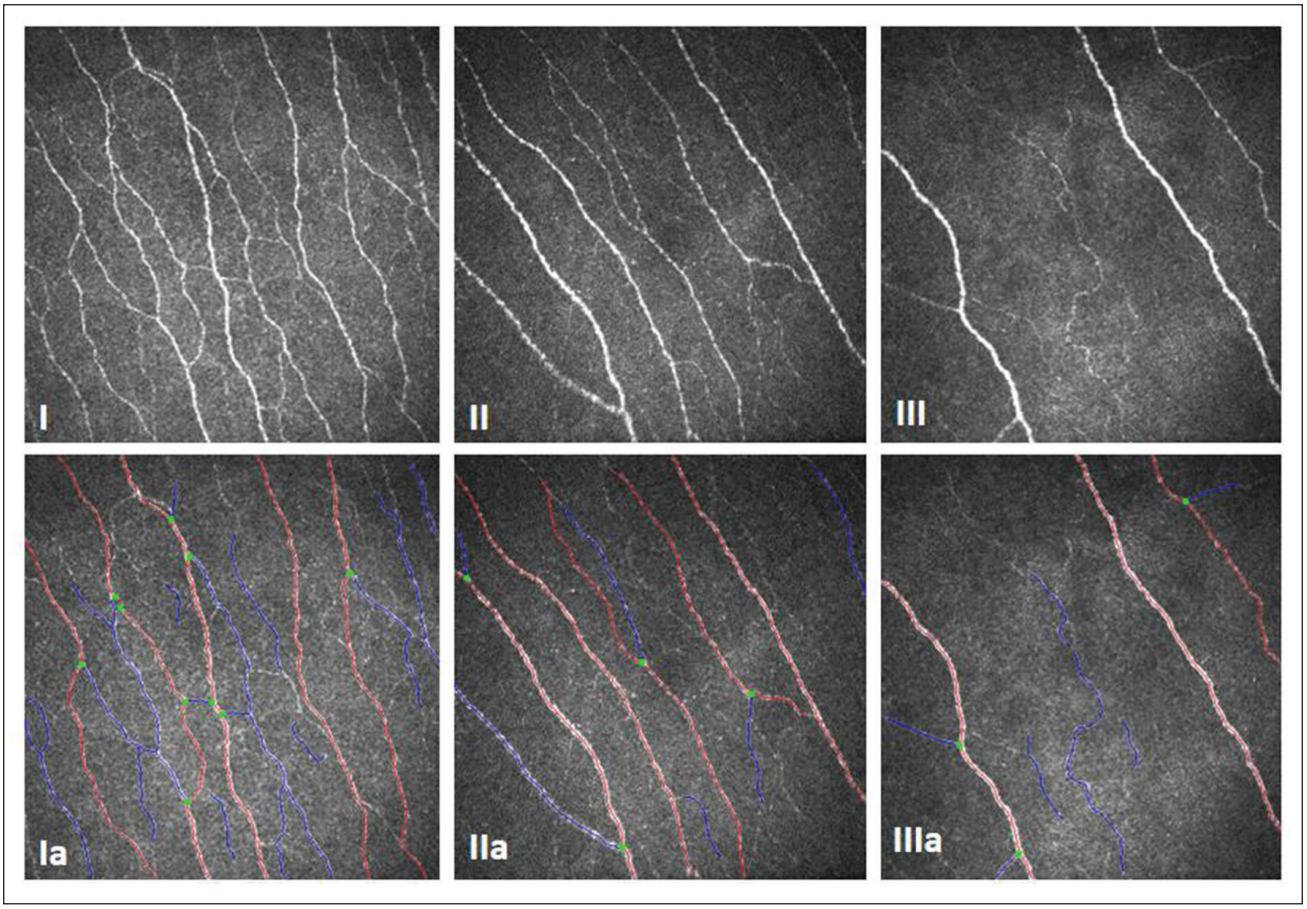

Figure 1. ***I and Ia: Images of a healthy 16-year-old adolescent.*** Original images of corneal sub-basal nerve plexus (I); Analysed images using CCMetrics software *(red: fiber; blue: branch; green: branch point)* showing normal corneal nerve fibre parameters *(fibre density: CNFD; branch density: CNBD; fibre length: CNFL)* (CNFD 31.2/mm^2, CNBD 62.5/mm^2, CNFL 21.1 mm/mm^2) (Ia); ***II and IIa: CCM images of 15-year-old boy with HbA1c 9% and T1DM duration of 10 years.*** Original images of corneal sub-basal nerve plexus (II); Analysed images showing reduced corneal nerve parameters (CNFD 18.7/mm^2, CNBD 38.7/mm^2, CNFL 16.0 mm/mm^2) (IIa); ***III and IIIa: CCM images in our patient*** *(described in case report)*. Original images of corneal sub-basal nerve plexus (III); Analysed images showing poor corneal nerve morphology in our patient (CNFD 16.8/mm^2, CNBD 28.7/mm^2, CNFL 11.0 mm/mm^2) (IIIa).

with IAH could prove to be an easy-to-perform and non-invasive surrogate test for the detection of underlying small nerve fibre abnormalities.

CONCLUSION

The present report highlights the potential clinical utility of CCM in detecting early small fibre abnormalities in T1DM and IAH. In the future, it would be interesting to perform longitudinal studies to evaluate if changes in CCM precede IAH or can predict the future risk of IAH in individuals with T1DM.

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Ethical Consideration
Patient consent was obtained before submission of the manuscript.

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

CRediT Author Statement
MB: Software, Data Curation, Writing – original draft preparation; **PM:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – review and editing, Visualization, Supervision; **MB:** Software, Data Curation; **SG:** Conceptualization, Methodology, Software, Visualization, Formal analysis, Investigation, Resources, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition.

Author Disclosure
The authors declared no conflict of interest.

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