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Autonomic neuropathy is associated with impairment of dynamic cerebral autoregulation in type 1 diabetes

N. Nasr [a,*], M. Czosnyka [b], F. Arevalo [c], H. Hanaire [d], B. Guidolin [e], V. Larrue [a]

[a] Service de Neurologie Vasculaire, Hôpital Rangueil, Toulouse, INSERM U858, Team 09, IFR31, Toulouse, France
[b] Academic Neurosurgical Unit, Addenbrooke's Hospital, University of Cambridge, UK
[c] Pôle de Psychiatrie Générale 31, Hôpital Gérard Marchant. 134, route d'Espagne, Toulouse, France
[d] Service de Diabétologie, Hôpital Rangueil, Toulouse, France
[e] Service de Neurologie Vasculaire, Hôpital Rangueil, Toulouse, France

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ABSTRACT

Hypothesis: The mechanisms underlying impairment of dynamic cerebral autoregulation in diabetes are not well known. Cardiovascular autonomic neuropathy (CAN) could contribute to dynamic cerebral autoregulation impairment. In this study, we assessed the association between CAN and impairment of dynamic cerebral autoregulation in patients with type 1 diabetes.
Methods: We evaluated dynamic cerebral autoregulation (DCA) in patients with type 1 diabetes and no history of cerebrovascular disease. DCA was assessed with transcranial Doppler using the correlation coefficient index Mx method. Mx was calculated from slow changes in mean cerebral blood flow velocity and mean arterial blood pressure. Increase in Mx indicates weaker DCA, with a threshold for impaired DCA above 0.3.
Moderate CAN was defined as reduced heart rate variability (HRV) on the following tests: deep controlled breathing, Valsalva maneuver or initiation of active standing. Severe CAN was defined as reduced HRV associated with orthostatic hypotension.
Results: 60 patients were included (M/F: 33/27; mean age ± SD: 46 years ± 11.5). 23 patients had moderate CAN and 15 patients severe CAN. DCA was impaired in 37 patients. CAN was associated with impaired DCA ($p = 0.005$). Impairment of DCA was more pronounced in patients with severe CAN ($p = 0.019$). Glycosylated haemoglobin (HbA1c) was associated with impaired DCA in univariate analysis ($p = 0.05$). In multivariate analysis, only CAN was associated with impaired DCA ($p = 0.007$) whereas HbA1c was not ($p = 0.161$).
Conclusions: CAN was associated with impaired DCA in type 1 diabetes. The magnitude of DCA impairment increased with the severity of CAN.

Autoregulation of cerebral blood flow is a homeostatic mechanism which is responsible for limiting the variations of cerebral blood flow when the arterial blood pressure (ABP) changes. The so-called static autoregulation refers to stability of cerebral blood flow when ABP is increased or reduced in a steady fashion on prolonged periods of time. The dynamic approach of cerebral autoregulation is based on the analysis of the rapid adaptive response of cerebral arteries to acute changes in ABP to restore cerebral blood flow (Panerai, 1998). Both static (Bentsen et al., 1975) and dynamic cerebral autoregulation (DCA) (Kim et al., 2008; Marthol et al., 2007) can be impaired in diabetes.

Cerebral autoregulation depends mainly on the myogenic tone of cerebral vessels. Increase in the myogenic tone enhances cerebral autoregulation whereas reduction in myogenic tone weakens autoregulation (Paulson et al., 1990). The autonomic nervous system plays a role in modifying the myogenic tone of cerebral vessels. Large cerebral arteries are innervated by sympathetic fibres originating from the superior cervical ganglia and parasympathetic fibres from the sphenopalatine and otic ganglia. Activation of sympathetic nerves from the superior ganglia elicits a powerful cerebral vasoconstriction, whereas the cerebrovascular parasympathetic system is a potent vasodilator upon stimulation (Hamel, 2006). DCA has been shown to be altered by the suppression of autonomic activity which has been obtained by perfusion of trimethaphan in healthy volunteers (Zhang et al., 2002). DCA has also been shown to be altered by the administration of prazosin, an antagonist of the noradrenergic alpha receptors which are responsible for sympathetically-mediated cerebral vasoconstriction (Ogoh et al., 2008). These results support an impact of autonomic nerves on cerebral autoregulation.

Impairment of cerebral autoregulation in diabetics could be due either to impairment of the autonomic nervous system (Mankovsky et al., 2003) which is common in diabetes (The DCCT Research Group, 1988), or to cerebral microvascular complications (Kim et al., 2008). Very few studies have looked for the association between cerebral

* Corresponding author. Service de Neurologie Vasculaire, Hôpital Rangueil, 1, av Prof Jean Poulhès, 31059 Toulouse Cedex 9, France. Tel.: +33 5 61 32 26 41; fax: +33 5 61 32 29 26.
E-mail address: nasr.n@chu-toulouse.fr (N. Nasr).

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autoregulation impairment and cardiovascular autonomic neuropathy (CAN) in diabetes (Mankovsky et al., 2003; Chiu et al., 2005). Interpretation of these studies is hampered by several limitations including small numbers, heterogeneity of the patients with regard to the type of diabetes, and the use of a non-validated method for cerebral autoregulation assessment. Also, available studies did not encompass the possible impact of microvascular complications on cerebral autoregulation.

In the present study, we assessed the hypothesis that impairment of cerebral autoregulation is associated with CAN in patients with type 1 diabetes.

1. Methods

1.1. Study population

Consecutive patients who were referred to our Neurosonology and Autonomic Nervous System Assessment Unit for cardiovascular autonomic nervous function testing were considered for inclusion. Patients referred to our unit previously had a positive clinical screening for CAN in the Diabetes Medicine Department where they had a regular assessment.

In patients who fulfilled the inclusion criteria, assessment of cerebral autoregulation was performed in addition to the cardiovascular autonomic nervous function testing.

Patients could be included if they were aged 18–70 years, and had type 1 diabetes. Exclusion criteria were type 2 diabetes, maturity-onset diabetes in the young (MODY diabetes), history of cerebrovascular disease, inadequate temporal acoustic bone window, any abnormality on transcranial Doppler (TCD) examination performed before inclusion suggesting an intracranial artery stenosis or a cervical carotid artery stenosis (Alexandrov et al., 1999; Wilterdink et al., 1997). Further patients were excluded when general conditions were present that could impair DCA (respiratory failure, hyperthermia, obstructive sleep apnea syndrome and sickle cell disease), or when severe untreated retinopathy was present as it prohibits the use of the Valsalva maneuver. Other exclusion criteria were cardiac failure, cardiac rhythm disorders, beta-blockers, medications that may increase the QT (diltiazem and verapamil), and treatment for orthostatic hypotension. All patients had a capillary blood glucose test in the 15 min that preceded DCA and CAN assessments. Patients with glucose level below 0.6 g/l or above 4 g/l were excluded.

We recorded the following data: duration of diabetes, result of the last glycosylated haemoglobin (HbA1c) measurement, microvascular and cardiovascular complications, peripheral neuropathy, smoking, hypertension, body mass index, snoring, and medications used.

Microvascular complications included retinopathy and nephropathy, which were searched for on regular check-ups in the Diabetes Medicine Department. Retinopathy was diagnosed by an ophthalmologist, and nephropathy was diagnosed using serum creatinine measurement and urinary albumin excretion (abnormal if persistently above 30 mg/day). It was considered to be a complication of diabetes if there was no evidence of another cause that could explain abnormal albumin excretion or renal function impairment.

We included in our analysis a group of control subjects composed of nine non-diabetic volunteers recruited in an earlier study on cerebral autoregulation. The control group was composed of 4 men and 5 women. The mean age $\pm$ SD was 49.1 years $\pm$ 5.3. The body mass index was 26.8 $\pm$ 2.7. One subject had hypertension, 3 had hyperlipemia and 5 were smokers (Nasr et al., 2009).

1.2. Assessment of dynamic cerebral autoregulation

Cerebral autoregulation assessment was performed using TCD, at rest, in supine patients, just prior to CAN assessment. The MCA was insonated unilaterally through the temporal bone at a depth of 50–55 mm with a 2-MHz probe using a DWL Multidop X2 (DWL, Germany). The probe was then fixed using a rigid headframe (Lam rack, DWL, Germany). DCA assessment was performed on the right side, except for patients who had a more accessible left temporal acoustic window.

Continuous monitoring of ABP was achieved using a servo-controlled finger plethysmograph (Finapres, Ohmeda, CO, USA) with the patient's left hand positioned at heart level. Finapres ABP values were cross-calibrated with an automated Dinamap monitoring system.

Mean ABP and mean cerebral blood flow velocities (CBFV) in the MCA were recorded over 10 to 20 min. Analog outputs from the pressure monitor and TCD unit (maximal frequency outline) were connected to an analog-to-digital convertor and were synchronized. ABP and CBFV signals were collected into a computer and were analyzed using the BIOSAN SOFTWARE (Biological Signals Analyser) version 2.2 developed by P. Smielewski and M. Czosnyka for data collection.

We assessed cerebral autoregulation with TCD using the dynamic approach in time domain and the Mx method. The Mx autoregulatory index is a correlation coefficient derived from the spontaneous slow variations of mean arterial blood pressure (mean ABP) and mean CBFV (Czosnyka et al., 1996; Lang et al., 2002). With band pass filtering, components of ABP and CBFV of periods from 20 s to 3 min are extracted. Mean values of these components are calculated as moving averages every 10 s (mABP and mCBFV). 30 consecutive moving samples of mABP and mCBFV are correlated with each other using Pearson correlation coefficient, producing temporary value tMx. This calculation is repeated every 10 s and tMx values from whole recording are averaged, producing final coefficient Mx. Altered DCA will manifest as an increase in Mx values. Mx close to +1 denotes that slow fluctuations in ABP produce synchronized slow changes in CBFV indicating defective DCA. Mx around 0 indicates that variations in ABP are not associated with variations in CBFV, indicating that DCA is preserved. Positive Mx values, particularly, Mx values above 0.3 indicate impaired autoregulation. Mx values $\leq$0.3 indicate normal autoregulation (Lang et al., 2002; Czosnyka et al., 2000). The magnitude of the increase of Mx reflects the severity of autoregulation impairment (Lang et al., 2002; Czosnyka et al., 2003). The Mx method has been validated against Aaslid's reference method for DCA assessment and against other methods that assessed DCA in several pathological situations (Smielewski et al., 1997; Piechnik et al., 1999; Gooskens et al., 2003; Aaslid et al., 1989; Lang et al., 2002; Lavinio et al., 2007).

1.3. Assessment of cardiovascular autonomic neuropathy

We used plethysmography for continuous ABP and heart rate (HR) recordings. Recordings of ABP and HR were computerized. HR variability was measured on deep controlled breathing (6/mn), Valsalva maneuver (Valsalva ratio), and initiation of active standing (30/15 ratio). The results of these three tests assessing HR variability were compared to age-adjusted values obtained from healthy volunteers who were previously examined in our unit.

Postural changes of ABP were analyzed in each subject during passive (head-up tilt test) and active standing using a Dinamap monitoring system which measured ABP every 30 s. Orthostatic hypotension was defined as a drop of a minimum of 20 mm Hg for systolic ABP or 10 mm Hg for diastolic ABP occurring during the first 3 min following active or passive standing (Consensus statement, 1996). The first measurement after standing was excluded. CAN was confirmed when a minimum of two of the afore-mentioned tests (orthostatic hypotension, heart rate variability on deep controlled breathing, Valsalva ratio or 30/15 ratio) indicated pathological response (Vinik and Ziegler, 2007).

One characteristic of CAN evolution in type 1 diabetes is that impairment of HR variability precedes orthostatic hypotension; patients with type 1 diabetes and orthostatic hypotension have a more severe CAN than patients with only impaired HR variability