Microvascular Perfusion Abnormalities of the Thalamus in Painful but Not Painless Diabetic Polyneuropathy

A clue to the pathogenesis of pain in type 1 diabetes

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OBJECTIVE—The pathogenesis of painful diabetic neuropathy (DN) remains undetermined, with both central and peripheral mechanisms implicated. This study investigates whether thalamic perfusion abnormalities occur in painful DN.

RESEARCH DESIGN AND METHODS—Eighteen subjects with type 1 diabetes (no DN = 6, painful DN = 5, painless DN = 7) and six healthy volunteers (HV) were recruited. Microvascular perfusion characteristics (relative cerebral blood volume [rCBV], flow [rCBF], and transit time [TTFM]) of the thalamus and caudate nucleus were assessed using magnetic resonance perfusion imaging. The caudate nucleus was chosen to serve as an in vivo control region.

RESULTS—Subjects with painful DN had significantly greater thalamic rCBV (means [SD]; painful DN, 228.7 [19.5]; no DN, 202.3 [25.8]; painless DN, 216.5 [65.5]; HV, 181.9 [51.7]; P = 0.04) and the longest TTFM (painful DN, 38.4 [3.6]; no DN, 35.3 [13.2]; painless DN, 35.9 [13.7]; HV, 33.7 [14.9]; P = 0.07). There was no significant difference in markers of caudate nucleus perfusion.

CONCLUSIONS—Painful DN is associated with increased thalamic vascularity. This may provide an important clue to the pathogenesis of pain in DN.
RESULTS—Subjects with painful DN (62.0 [3.9]) were significantly older than those with no DN (44.9 [7.1]) and HV (45.8 [14.7]; P = 0.03; painful DN vs. no DN, P = 0.005, 95% CI 5.7–28.5; painful DN vs. HV, P = 0.01, 95% CI 3.8–28.5). Subjects were matched for BMI (HV 26.7 [5.2], no DN 30.2 [3.9], painless DN 25.6 [2.3], painful DN 31.1 [5.1], P = 0.08) and HbA1c, (no DN 8.4 [0.2]), painless DN 8.9 [0.9], and painful DN 7.7 [0.9]; P = 0.71). Subjects with painful DN (NCS 31.0 [9.5]) and painless DN (21.8 [15.5]) had comparable severity of neuropathy, which were greater than those with no DN (1.0 [1.1]). There was no difference in the presence of microvascular complications (diabetic retinopathy data from retinal screening database; painful DN [n = 3], painless DN [n = 2], no DN [n = 2], and diabetic nephropathy based on albumin:creatinine ratio; painful DN [n = 3], painless DN [n = 3], no DN [n = 1]) between subjects.

Figure 1 is a composite time profile ofthalamic perfusion of the study groups. The bolus arrival time (in seconds) was delayed in both neuropathy subgroups (painful DN 28.6 [1.6] and painless DN 27.3 [2.4]) compared with HV 23.6 (6.3) and no DN 24.2 (5.9), P = 0.7, χ² = 1.3. Overall group comparison showed that subjects with painful DN (rCBV 228.7 [19.5]) have the tallest peak concentration of Gd-DTPA and significantly greater mean thalamic rCBV compared with HV (181.9 [51.7]), no DN (202.3 [25.8]), and painless DN (216.5 [65.5]); P = 0.04, χ² = 8.3). Subjects with painful DN (TTFM 38.4 [3.6]) had the longest thalamic TTFM (in seconds) compared with the other study groups (HV 33.7 [14.9]), no DN 35.3 [13.2], painless DN 35.9 [13.7]; P = 0.07, χ² = 6.9). Caudate nucleus perfusion markers were not significantly different between groups.

CONCLUSIONS—Painful DN is the most distressing complication of diabetes (11), but unfortunately current treatments are often ineffective (12). This may be as a result of our poor understanding of the pathophysiological processes involved (13). Using established MR perfusion techniques, we demonstrated increased thalamic vasculariﬁcation (increased rCBV) with sluggish ﬂow (prolonged TTFM) in painful DN, possibly reﬂecting underlying vasodilatation. Delay in bolus arrival time in both neuropathy subgroups reﬂects the burden of underlying vascular disease. Similar perfusion abnormalities have been described in the sural nerve (14). Despite this, there remains clear difference in the perfusion profiles of both painful and painless DN. There were no signiﬁcant differences in the microvascular perfusion characteristics of the caudate nucleus. Unlike the caudate, the thalampus plays a central role in modulating/processing somatosensory information that is relayed to the cerebral cortex (8).

We have previously reported that preservation of thalamic neuronal function may be a prerequisite for the perception of pain in DN (2). Hyperecitable thalamic neurons have since been reported to contribute to neuropathic pain in experimental diabetes (15). Thus thalamic neurons can act as central generators or amplifiers of pain in diabetes. Our ﬁnding of elevated thalamic perfusion may be related to increased neuronal activity.

Limitations of the current study include an age spread of several years between cohorts, and age is a factor in cerebral hypoperfusion. Paradoxically, however, subjects with painful DN comprised the oldest cohort but possessed the greatest thalamic rCBV. This would suggest comparative hyperperfusion rather than hypoperfusion. Interestingly, the difference in thalamic microvascular perfusion between painful and painless DN is not reﬂected by microvascular disease burden elsewhere with comparable prevalence of minimal retinopathy and neuropathy in both groups.

Our goal was to assess whether thalamic perfusion abnormalities are present in DN. The data presented here at least preliminarily support this view. A larger study with sample sizes of 12 from each of the four groups would achieve 91% power to detect signiﬁcant differences among the groups. Future MR perfusion studies may lead to identiﬁcation of objective hemodynamic correlates of painful DN enabling the targeting of speciﬁc components of the pain matrix pharmacologically, hopefully resulting in the development of more effective and better tolerated drugs.

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