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Are cardiac syndrome X, irritable bowel syndrome and reflex sympathetic dystrophy examples of lateral medullary ischaemic syndromes?

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Summary Altered pain appreciation and autonomic function are hallmarks of Cardiac syndrome X, Irritable bowel syndrome and Reflex sympathetic dystrophy. Both pain appreciation and autonomic function are controlled by the lateral medulla. This hypothesis proposes that lateral medullary ischaemia at a microvascular level is responsible for these syndromes and could also be linked to other conditions where autonomic dysfunction is a major feature such as late-onset asthma, type 2 diabetes and essential hypertension. Autonomic function is controlled by the nucleus tractus solitarius, which acts as the main visceromotor nucleus in the brain stem regulating vagal tone. It is particularly susceptible to ischaemia since it is highly metabolically active and lies in a medullary arterial watershed zone. The anatomical route of the vertebral artery through cervical vertebra makes it vulnerable to injury from whiplash with or without any genetic predisposition to atheroma formation. This could make microvascular occlusion commonplace and a plausible explanation for the above syndromes. Ischaemia rather than infarction occurs because of the excellent collateral blood supply in the brainstem. In support of this hypothesis, a new Transcranial doppler ultrasonography arterial signal has been described called small vessel knock, the ultrasound signal of small vessel occlusion. Recent evidence has shown that ultrasound targeting of this signal in the vertebral artery improves clinical symptoms in these syndromes which supports this hypothesis. Two such cases are discussed.

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The caudal lateral/posterior medullary region (CLM) of the brain stem is critical to the control of blood pressure, heart rate, breathing, alertness, vomiting, gut motility and viscerosensory percep-

tion. It receives blood supply from perforating branches of both the intracranial segment of the vertebral artery (V4) and the main branch of V4, the posterior inferior cerebellar artery (PICA) [1]. A functioning CLM is needed to appreciate pain ipsilaterally and contralaterally in the face (spinal tract of V and trigeminothalamic fibres,

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respectively) and contralaterally in the arm, chest (spinothalamic nerve fibres in deep lateral medulla) and leg (spinothalamic nerve fibres in the superficial lateral medulla). Adjacent to these spinothalamic tracts lies the nucleus and tractus solitarius (NTS), which receives visceromotor afferent nerve fibres from the carotid sinus and glossopharyngeal nerve as part of the baro-receptor reflex, along with other afferent vagal fibres from the heart, lungs and gut. The NTS relays signals to the motor nucleus of the vagus, increasing vagal tone, to the thalamus and to the spinal cord inhibiting sympathetic outflow [2].

CLM infarction, which normally results from occlusion of V4 and the PICA produces the lateral medullary or Wallenberg's syndrome (LMS). Classical LMS presents with ipsilateral and contralateral loss of pain sensation in the face and body, respectively, diplopia/visual blurring, vertigo, hoarseness, ataxia, nausea and vomiting, unilateral occipital headache, without hemiplegia or loss of touch sensation [3]. However, the PICA also supplies below the decussation and in 6–10% of cases mild ipsilateral hemiplegia and hemianaesthesia can occur (see Case 1.) [4]. Good brainstem collateral blood supply often results in a partial LMS and hypersensitivity to pain due to ischaemia rather than infarction has also been reported [5]. The NTS is particularly sensitive to ischaemia, since it has an intense metabolic activity and lies in a medullary watershed zone [6], and so abnormal vasomotor control, sweating, cardiac rhythm, blood pressure and gut motility have all been reported in the LMS [3]. These variations in presentation provide diagnostic difficulty and not surprisingly the LMS is often under/misdiagnosed.

The causes of cardiac syndrome X (CX) [7] and irritable bowel syndrome (IBS) [8,9] are unknown but both are characterised by altered visceral hypersensitivity to pain (during intracardiac balloon inflation in CX and balloon inflation in the gut in IBS). In reflex sympathetic dystrophy (RSD) [10] there is abnormal pain appreciation in a limb. In all three conditions there appears to be an imbalance between parasympathetic and sympathetic activity [7–10]. It has been proposed that this leads to arrhythmias, ST and T wave changes on an electrocardiogram both at rest and during exercise in CX and altered bowel habit in IBS, respectively. In RSD, this results in abnormal vasomotor tone.

In this hypothesis, it is proposed that altered pain sensitivity and autonomic dysfunction found in these syndromes could be explained by CLM ischaemia. Mild ischaemia, could produce depolarisation and neuronal hypersensitivity, which would

increase pain perception for both the body and/or viscera (spinothalamic neurones) and by increasing NTS neuronal activity result in increased vagal motor activity (bradycardia and/or increased bowel habit) and decreased sympathetic output (lowered blood pressure and/or increased limb vasodilatation). More severe ischaemia could produce the opposite effects due to hyposensitivity of these neurones. Different syndromes occur because the NTS and spinothalamic neurones at different levels of the brainstem have distinct functions and medullary autonomic function is asymmetrical [11]. However, a common ischaemic aetiology would explain known syndrome overlap and variations in the degree of ischaemia would explain why opposing symptoms can be found in the same patient on different occasions. It is also possible that NTS hypersensitivity could increase bronchial hyperresponsiveness worsening or causing late onset asthma [12] and hyperinsulinism in type 2 diabetes [11], underactivity could be involved in the development of essential hypertension [13].

Both CX and IBS are common conditions (up to 10–20% of patients with suspected coronary artery disease have normal coronary angiograms [14]; irritable bowel prevalence varies on criteria but has been reported to affect 1 in 10 adults [15]) and patients often present in their thirties, with no vascular risk factors and without florid neurological signs. In a busy district hospital such as the Borders General Hospital, patients who have these syndromes and no vascular risk factors often have had a previous history of significant whiplash or head injury. Features of LMS are found in all three syndromes but these neurological signs tend to be ignored when the primary presentation is with chest pain or bowel symptoms. However, for ischaemia of the CLM to be the cause of these syndromes, branch occlusions of V4 and the PICA would have to occur frequently in an age group where stroke is uncommon and since there have been no reports of any associated abnormality on CT/MRI scan, at a microvascular level (small vessel occlusion). MRI-negative stroke-like episodes [16] are not uncommon and it is also known that arteriosclerosis can start in the thirties [13]. These patients may have a genetic cause since the heritability of cerebral small vessel disease (cSVD) is estimated at 73% [17] and recently the angiotensinogen B haplotype has been associated with cSVD [18]. The association of whiplash in low risk patients is interesting and could mean that this known cause of artery dissection [5] may also cause microvascular occlusion. The vertebral artery may be especially vulnerable to injury due to its long transforaminal course. Atheroma could then

develop at the injury site with subsequent atherothrombosis and microvascular occlusion of branches of the vertebral artery and PICA developing at a later date. Whiplash in the population is not infrequent and so this mechanism could make small vessel vertebral artery/PICA branch occlusion commonplace.

In support of a microvascular ischaemic aetiology for these syndromes, two cases of CX showing overlap with RSD and IBS will now be discussed. In both cases, a new microvascular abnormality, small vessel knock (SVK), was found in their vertebral arteries using transcranial Doppler ultrasonography (2 MHz Ezdop) (TCD). SVK has recently been reported in a series of patients with MRI-negative LMS [19] and it is proposed that SVK is the ultrasound signal obtained from small vessel occlusion. Targeting SVK with ultrasound using a new technique can result in clinical recovery over an extensive time window, which challenges current thoughts on the ischaemic penumbra [20]. The reversibility of these stroke-like deficits suggest that chronic ischaemia due to small vessel occlusion can occur in LMS patients without resulting in infarction or cytotoxic oedema (MRI invisible). In the cases presented, SVK insonation resolved their symptoms and provides preliminary but exciting evidence linking SVK to these syndromes.

Case 1. Case 1 is a 45-year-old man who presented with sudden onset of double vision, altered balance and central chest pain associated with a 2-week history of right occipital headache and tiredness. He is an obese ex-smoker with no other vascular risk factors. He was treated with streptokinase but subsequent cardiac enzymes were normal. Further examination confirmed mild diplopia on lateral gaze, abnormal balance and reduced sensation to touch and mild weakness of his left

hand side. He also had reduced pain sensation on his right arm. During admission he developed dramatic changes to the colour of his left arm and was treated for a suspected limb embolism. His exercise test (ETT) was positive but a subsequent coronary angiogram was negative, as were a CT, MRI, MRA scan (including the aortic arch) and an echocardiogram. TCD revealed SVK in both vertebrals and the basilar artery with florid SVK signals in the left vertebral artery at 50 and 66 mm (see Fig. 1). Over the next month he had two further episodes of classical cardiac chest pain each associated with altered pain sensation and increased bowel frequency (6×/day)(IBS symptoms). On each occasion SVK insonation was associated with clinical improvement.

Case 2. Case 2 is a 48-year-old lady with familial hypercholesterolaemia and IBS with a strong family history of ischaemic heart disease who presented with a 2-week history of intermittent central chest pain. Minor anterolateral ST depression was found on ECG and an ETT was positive. Cardiac enzymes and coronary angiography were normal. Further review revealed a history of sudden onset of headache, blurred vision, left arm pain and increased abdominal pain and bowel frequency (IBS symptoms). Detailed neurological examination revealed double vision upon right lateral gaze and increased temperature and pain sensation on the left arm and right side of her face. An MRI was negative but TCD revealed SVK in the right vertebral and basilar arteries (not shown). Insonation resolved all neurological symptoms, chest pain and IBS symptoms. Over the next 3 months, this patient had two identical episodes each resolved by SVK insonation. This patient describes her recovery in a recent BBC Radio Scotland programme called "Guinea pigs" [21].

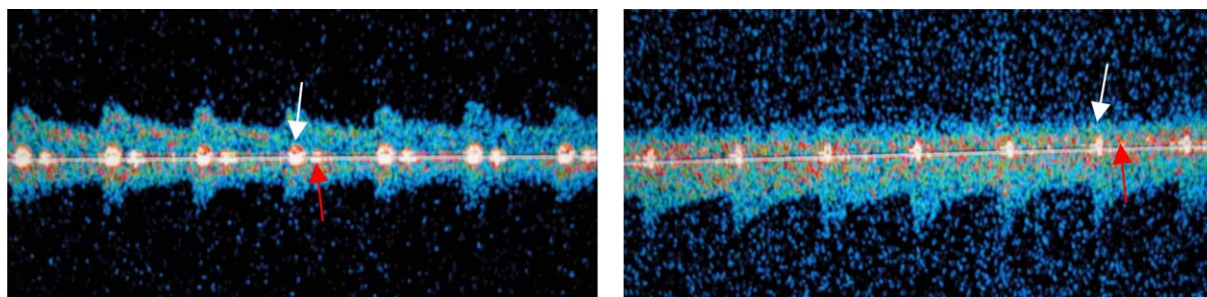


Figure 1 Shows left vertebral artery TCD spectra from Case 1 at 50 mm (left of figure) and around the origin of the PICA at 66 mm (right of figure) through the transforaminal window. SVK [20] can be identified as a baseline hyperintensity signal occurring during each cardiac cycle at peak systole (white arrow) followed by a further hyperintensity signal occurring at aortic valve closure (red arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Conclusions

In this hypothesis, microvascular ischaemia of the CLM due to minor injury of the vertebral artery could be responsible for the abnormal pain appreciation and autonomic imbalance, consistently found in CX, IBS and RSD. In support of this hypothesis, preliminary evidence is shown that a new TCD microvascular abnormality, SVK, can be found in association with these syndromes and clinical improvement occurs when SVK is targeted by ultrasound. This hypothesis and the potential benefit of TCD in these syndromes now need to be confirmed by randomised control trials.

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