Prediction of Sudden Cardiac Death in Diabetic Autonomic Neuropathy

TO THE EDITOR: Sudden cardiorespiratory arrests and unexpected deaths have been observed in patients with diabetes mellitus complicated by autonomic neuropathy (DAN) (1). The pathogenetic link between DAN and sudden demise remains uncertain. We have recently reported that patients with DAN frequently have a prolongation of the corrected QT (QTc) interval (2), known to be associated with malignant ventricular arrhythmias (3). Metaiodobenzylguanidine (MIBG) appears to act as an analog of the adrenergic neurotransmitter, norepinephrine, and we have shown that concentrations of radiolabeled MIBG reflect the functional integrity of adrenergic neurons in the heart (4,5). In five patients with generalized autonomic neuropathy, the concentrations of iodine-123 metaiodobenzylguanidine ([123I]MIBG) in the heart were markedly reduced; the subject of this manuscript was included in this group (5). We report herein our observations of a patient with DAN who had QTc prolongation and an abnormal MIBG scan who subsequently died suddenly. Our observations prompt us to suggest that these measurements may identify patients at risk.

Case Report

A 36-yr-old nonobese white male 5 ft 7 in. tall, weighing 142 lb with a 15-yr-history of insulin-dependent diabetes mellitus (IDDM) was cared for in the Endocrine Clinic of the University of Michigan Medical Center. Resting blood pressure was 80/64 mmHg and heart rate 96 bpm. He had a mixed sensory/motor polyneuropathy, gastroparesis diabeticorum (gastric emptying time 55 min, N < 17 min) and background retinopathy, but did not have renal disease, or clinical evidence of cardiac disease. Cholesterol was 132 mg/dl, triglyceride 101 mg/dl and glycohemoglobin 9.8 g (n 6–7%). Supine norepinephrine was 196 pg/ml which rose to 369 pg/ml after standing for 15 min. His resting cardiac ejection fraction was 61% and did not increase with maximal exercise.

As part of a research protocol approved by the Institutional Review Board of the University of Michigan, the patient underwent testing for cardiac autonomic neuropathy (CAN), as previously reported (6), which demonstrated CAN with four of five values abnormal (Table 1). A rest and maximal exercise electrocardiogram were normal with the exception of a prolonged QTc interval of 460 msec and 470 msec, respectively (normal <440 msec (7)). A maximal exercise myocardial perfusion scan with tomographic thallous-201 chloride imaging was performed as previously described (6) and was normal (Fig. 1A) strongly suggesting the absence of coronary artery disease. A nonuniform loss of cardiac adrenergic innervation was indicated by a nonhomogeneous and abnormal uptake of [123I]MIBG (Fig. 1B) compared with that in a normal subject (Fig. 1C).

The patient was followed for 5 mos following completion of the research protocol in the Endocrine clinic and was free of cardiac symptoms. At that time, he was observed by his family to awaken in apparent good health only to be found 15 min later pulseless and apneic. Resuscitative efforts were unsuccessful. An autopsy was not permitted.

Discussion

The case reported herein provides further evidence linking DAN, QTc interval prolongation, and sudden cardiac death. We have previously reported a cohort of patients with IDDM and DAN in whom abnormal prolongation of the QTc interval was frequent and was linearly related to the extent of DAN (2). In 30 patients with insulin dependent diabetes mellitus, without evidence of cardiovascular disease, cardiac autonomic neuropathy was found in 17. The corrected QT interval (QTc) (QTc = QT/RR) was prolonged (>440 msec) at rest (447 ± 6 versus 405 ± 2 msec, p < 0.0001) and peak exercise (15/17) (468 ± 6 msec, p < 0.001) in normal healthy controls. There was a direct correlation between the extent of cardiac autonomic neuropathy and the QTc interval (r 0.71; p <0.001) (2). Our patient had a QTc interval of 460 msec at rest and 470 msec at peak exercise suggesting that he may have cardiac sympathetic imbalance and be predisposed to greater risk of sudden arrhythmia and death. Our patient further had scintigraphic studies with the norepinephrine analog [123I]MIBG directly demonstrating abnormal sympathetic innervation of his heart, presumably resulting from DAN. While the occurrence of sudden death in this patient may be coincidental, it is reasonable to propose that the prolonged QTc interval predisposed him to malignant ventricular arrhythmias (3). It may thus be that QTc interval prolongation may identify those individuals with cardiac autonomic neuropathy who can be shown to be at risk by MIBG scans and are, therefore, candidates for close surveillance. The frequency of this relationship in a larger population of patients with IDDM is unknown and examination of more patients will be needed to confirm these preliminary observations.

Acknowledgments

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<tr>
<th>TABLE 1</th>
<th>Abnormal</th>
<th>Case study</th>
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<tr>
<td>Resting heart rate (HR) (bpm)</td>
<td>≥100</td>
<td>96</td>
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<tr>
<td>Beat to beat HR variability (bpm)</td>
<td>≤10</td>
<td>12</td>
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<tr>
<td>Valsalva ratio</td>
<td>≤1.10</td>
<td>1.06</td>
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<tr>
<td>HR response to standing (30-15 ratio)</td>
<td>≤1.00</td>
<td>1.00</td>
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<tr>
<td>Orthostatic systolic pressure drop (mmHg)</td>
<td>≥30</td>
<td>36</td>
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* See Ref. (5).
FIGURE 1
Single photon emission tomographs were made with a GE 900 camera attached to a star computer system, 18 hr after the intravenous injection of 9 mCi [123I]MIBG or 3 hr after the injection of thallous-201 (99mTc). The short axis images are construction of 1.2 cm sections taken through the midportion of the heart. A: Tomographs made from a MIBG scan in a normal man; both right (on the left of the image) and left ventricles and their respective cavities are seen. Radioactivity in the liver can be seen below the heart. B: Tomographs made from the MIBG scan in the patient with DAN who died suddenly. There is absent uptake in the posterior region of the left ventricle (large arrow) as well as the right ventricle (small arrow), providing evidence of non-uniform loss of adrenergic neurons and an imbalance in adrenergic innervation. C: Tomographs made from the 99mTc scan in the patient whose images are shown in B. This image is constructed from sections at the same level as those in B and is normal. Although this image was made with the patient at rest, exercise induced no abnormality.

References

Intense Bilateral Breast Uptake of Gallium-67

TO THE EDITOR: In a recent article in this journal, Vazquez et al. (1) presented a case of intense bilateral breast uptake of gallium-67. The patient had a hypothalamic granuloma and a high prolactin level. This high prolactin level was felt by the authors to be the cause of the intense uptake. The authors further implied that high prolactin levels should be suspect whenever such intense bilateral symmetrical breast uptake is seen.

We have observed a gallium scan in a 78-yr-old male that showed intense uptake bilaterally in breast tissue, with increased uptake in the left hilar region and possibly very mildly increased uptake in the right hilar region (Fig. 1). He had had a previous transurethral prostatectomy and bilateral orchidectomy for carcinoma of the prostate. He was placed on diethylstilbestrol following surgery. The gallium scan was requested to assess activity of pulmonary fibrosis seen on chest x-ray. The gallium scan suggested that there was mildly active disease in the left hilar region and possibly also the right hilar region.

The chest x-ray showed bilateral gynecomastia and mild bilateral diffuse fibrotic changes.

Unfortunately a prolactin level was not available for this patient. Clinically this patient was not suspected of having a pituitary or suprasellar tumor.

Do Vazquez et al. have any similar cases to indicate that hyperprolactinemia and not estrogen is the cause of intense breast uptake of gallium?