Original Article

Type 2 diabetes mellitus: A central nervous system etiology

Peter J. Jannetta, Lynn H. Fletcher¹, Peter M. Grondziowski², Kenneth F. Casey³, Raymond F. Sekula Jr.¹

Department of Neurosurgery, Allegheny General Hospital, 420 East North Avenue, Suite 302, ¹Department of Neurosurgery, ²Center for Diabetes and Endocrine Health, Allegheny General Hospital, Pittsburgh, PA USA 15212, ³Oakwood Southshore Hospital, Department of Neurosurgery, Trenton, MI USA 48201

E-mail: *Peter J. Jannetta - pjannett@wpahs.org; Lynn H. Fletcher - lfletche@wpahs.org; Peter M. Grondziowski - pgroandzi@wpahs.org; Kenneth F. Casey - kenneth.casey@oakwood.org; Raymond F. Sekula Jr. - rsekula@wpahs.org

*Corresponding author

Abstract

Background: Insulin resistance (hyperinsulinemia) is said to be the signal event and causal in the development of type 2 diabetes mellitus. Pulsatile arterial compression of the right anterolateral medulla oblongata is associated with autonomic dysfunction, including "driving" the pancreas, which increases insulin resistance causing type 2 diabetes mellitus. In this prospective study, we hypothesize that decompressing the right cranial nerve X and medulla will result in better glycemic control in patients with type 2 diabetes mellitus.

Methods: Ten patients underwent retromastoid craniectomy with microvascular decompression for type 2 diabetes mellitus. Patients were followed for 12 months postoperatively by blood glucose monitoring and studies of glycemic control, pancreatic function and insulin metabolism. No changes in diet, weight or activity level were permitted during the course of the project.

Results: Seven of the 10 patients who received microvascular decompression for type 2 diabetes mellitus showed significant improvement in their glucose control. This was noted by measurement of diabetes markers and decrease of diabetes medication dosages. One patient was completely off diabetes medication, while attaining euglucemia. The other 3 patients did not improve in their glucose control. The body mass index of these 3 patients was higher (mean, 34.4) than those with better outcomes (mean, 27.9).

Conclusion: Arterial compression of the right anterolateral medulla appears to be a factor in the etiology of type 2 diabetes mellitus. Microvascular decompression may be an effective treatment for non-obese type 2 diabetes mellitus patients.

Key Words: Body mass index, diabetes mellitus, lateral medullary, microvascular decompression, type 2 diabetes, vascular cross-compression

INTRODUCTION

Over the past 45 years, we have studied pulsatile vascular compression of the cranial nerves. We demonstrated that a number of hyperactive dysfunction syndromes were not only caused by vascular compression but that they could be relieved without loss of function by mobilizing the offending blood vessel or vessels away from the
nerve (microvascular decompression, MVD). It is now generally accepted in the international neurosurgical community that vascular cross-compression causes cranial nerve hyperactive syndromes. These include, among others, trigeminal neuralgia, hemifacial spasm, vertigo and disequilibrium, Miniere’s disease, glossopharyngeal neuralgia and spasmodic torticollis. In 1973 the first observations were made on essential hypertension, which proved to be a vascular compression syndrome of the left anterolateral medulla. The vagus nerve is the only cranial nerve with an asymmetrical distribution. The vagal nuclei are affected by increased activity in the right vagal brainstem nuclei. The pancreas is partly innervated by the right vagus nerve by means of the hepatic and celiac branches. It may be affected by increased activity in the right vagal brainstem nuclei. We studied the right anterolateral medulla oblongata for the presence of arterial compression in 15 consecutive patients operated upon for right-sided cranial nerve vascular compression syndromes. A preliminary retrospective study showed that all 15 patients with type 2 diabetes had arterial compression of the right anterolateral medulla oblongata and that some could be relieved of their high blood sugar. A controlled prospective study was carried out.

The present study extends the above data regarding the cranial nerve and hypertension to include autonomic dysfunction (type 2 diabetes mellitus [DM]) as a result of arterial elongation and pulsatile compression of the right anterolateral medulla oblongata.

Metabolic syndrome, insulin resistance and type 2 diabetes are all related to neural loop feedback dysfunction. Multiple metabolic changes are seen in these syndromes. Recent work revealed that the neuropeptides, especially the kinins and their C-protein–coupled receptors (B1, B2), are up-regulated in the medullary regions of the human brainstem. These changes are seen in both hypertensive and diabetic specimens. These data implicate a regulatory role for these proteins in autonomic, motor and cardiovascular centers in the human so afflicted. In diabetic rats, glucose transporters (GLUT) and accompanying mRNA are increased in the medulla oblongata, especially in the area of the ninth cranial nerve level of that structure. In diabetes-induced animals, the monoamines, especially norepinephrine and serotonin, are seen to increase as a function of the length of time for the process. This data suggests the progressive nature of diabetes is related to the progressive changes in the regional concentrations of specific brain monoamines, especially norepinephrine. Infusion of norepinephrine in the lateral hypothalamic area (LHA) increases insulin secretion via increased vagal activity. Microinjection of glucose in this region results in efferent discharges in the right vagus, especially the pancreatic branches. We found that decompression of the area of the brainstem involved with the vagal innervation reduced the downstream action of this vagal overactivity.

Our preliminary report was a retrospective study in which we performed MVD of the medulla in 15 consecutive patients with type 2 DM. We found that we not only had to relieve the pulsation but also the distortion of the brainstem due to the compression. Therefore, we developed a device which when placed against the medulla decreases both arterial pulsation and distortion.

**METHODS**

Ten patients with type 2 DM which was steadily progressive volunteered for this study, which was approved by the Institutional Review Board (IRB) on the basis of our prior preliminary study and our minimal morbidity and rare mortality (0.01%) in over 6,000 of these operations. The major decision we made was to operate on persons with no other symptoms such as facial pain, which if relieved might confuse the result of the medullary decompression on the DM.

Ten patients with type 2 DM who were still making insulin, verified by C-peptide measurements, and had visible right lateral medullary compression by arterial loops on MRI scan underwent right retromastoid craniectomy and microvascular decompression of the medulla using previously described technique of exposure (5, 6, 9, 21) and an innovative, patented implant [Figures 1-3]. A small (2.0 x 2.5 cm) low lateral retromastoid craniectomy was performed with the patient in the contralateral lateral decubitus position. The head was supported with a three-point head holder. After opening and retraction of the dura using stay sutures, the cerebellum was gently supported with a microsurgical retractor over a rubber dam and cottonoid. The medulla and cranial nerves X and XI were explored. The arterial loop was mobilized and then held away from the neural tissue using the double implant. Patients were followed for 12 months postoperatively. No changes in diet, weight or activity level were permitted during the first 12 postoperative months of the project. An addendum to
the study protocol was approved by the IRB for follow-up to continue for another 12 months. However, not all patients agreed to participate in the extra 12 months.

The presence or absence and degree of arterial compression at operation were evaluated and recorded independently by the principal investigator and independently by neurosurgical colleagues.

The patients, 9 men and 1 woman, ranged in age from 43 to 63 years (mean age, 52.9 years) at the time of operation. Known duration of DM ranged from 1 to 20 years (mean, 6.8 years).

**MRI Grading**

MRI grading was performed preoperatively and postoperatively. Postoperative scans were performed 1 year postoperatively. The preoperative result was blinded at the time of the postoperative grading.

The scale used for grading was based upon which artery was compressing, designated by Roman numerals I-IV; and the amount of compression by the artery, designated by A-D, and O equaling ‘no artery adjacent to medulla’ — type I: vertebral artery (VA); II: posterior inferior cerebellar artery (PICA); III: both VA and PICA; IV: other; and compression grading O: no artery adjacent to medulla; A: artery proximate to medulla; B: artery mildly compressing medulla; C: artery moderately compressing medulla; D: artery severely compressing medulla.

**2-Hour Postprandial Glucose**

Two-hour postprandial (2-hr pp) blood glucose levels (meal study) were measured preoperatively while patients were taking their diabetes medications, and also after they had gone through a ‘washout’ period of 1 week while not taking their diabetes medications. The first 3 subjects did not have the preoperative testing done with medications as this test was added to the protocol after they had been operated upon. Follow-ups of the meal study with medications were done at 3 and 6 months postoperatively. The meal study without medications was repeated at 12 months postoperatively.

The meal study that was done after a 1-week washout period of all diabetes medications was completed by all 10 participants preoperatively and 12 months postoperatively. Patients were admitted to the clinical research unit the night before their testing, where they received a balanced meal for dinner, based on their BMI, and then nothing by mouth after midnight. A radioactive glucose isotope 3-3H-glucose was infused intravenously for 3.5 hours (210 minutes) through “0” time. Standardized liquid breakfast of a commercial product, 7 kcal/kg, was consumed at 0 time. Blood samples were taken from an intravenous line (in the arm opposite the one that was used for the
isotope infusion) every 15 minutes, starting at 30 minutes before ingestion of liquid meal through 120 minutes after ingestion. Samples were then taken at 30-minute intervals for the following 2 hours.

At the preoperative, 3-month, 6-month and 12-month meal studies, serum insulin, Hemoglobin (A\(_1c\)), weight and medication audits were performed. Patients were instructed to make no changes in diet or exercise during the study period.

Plasma glucose levels were measured with the use of the YSI 2300 STAT glucose analyzer (Yellow Springs Instruments). Serum insulin levels were measured with the use of Immulite 2000 (DPC Diagnostic Products, Corp.) Hemoglobin A\(_1c\) levels were measured using Bio-rad variant 21 and Phospholipase C (PLC).

Normal nondiabetic levels that were used for the metabolic assessments: FPG: 70-110 mg/dL; A\(_1c\): 4.0%-6.4%; serum insulin: <25 µU/mL (microunits per milliliter); two-hour postprandial plasma glucose: <140 mg/dL.

**RESULTS**

Results for individual lab, weight and medication measurements have been segregated into two different groups of ‘Good Responders’ (\(n = 7\)) and ‘Failed Responders’ (\(n = 3\)). Good responders’ inclusion criteria required that overall response with regard to glycemic control either improved or did not worsen at the 12-month postoperative follow-up. Failed responders had no slowing in the natural progression of diabetes [Tables 1-5, Graphs 1, 2].

**MRI grading**

MRI findings in 10 patients are tabulated in Table 1. At intraoperative visual evaluation, the compression-distortion was more severe than seen on MRI scans in 9 of the 10 patients. The compression-distortion severity was the same on scan and intraoperatively in subject #3. MRIs performed postoperatively revealed improvement in the amount of compression-distortion in 9 of the 10 patients. Four of the patients had no visible compression, while 5 patients showed only mild distortion attributed to the device used at operation. The postoperative MRI of subject #9 demonstrated more compression-distortion than the preoperative MRI. We are unsure if this was actually due to the implant.

**Blood chemistry**

The changes in hemoglobin A\(_1c\) (A\(_1c\)) following MVD are collated in Table 2. A\(_1c\) was improved at 12 months in 7 patients and worse in 3 patients. Change in weight was minimal and had no effect on change in A\(_1c\). A body mass index (BMI) over 32 correlated with failure to improve in 3 patients. Graphs 1 and 2 are scattergrams of BMI and weight with A\(_1c\) changes.

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**Table 1: MRI grading**

| Subject | Preop. MRI compression | OR compression | Postop. MRI compression |
|---------|------------------------|----------------|------------------------|
| 1       | II C (II C)*           | III C          | II A/(B) (I/implant?)   |
| 2       | III B                  | IV C           | I A/(B)                |
| 3       | III C                  | III C          | I A/(B)                |
| 4       | I C                    | I D            | 0                      |
| 5       | I C                    | I D            | 0                      |
| 6       | IV B                   | IV C           | 0                      |
| 7       | I C                    | III C          | II A                   |
| 8       | III B                  | III C          | I A/(B)                |
| 9       | III B                  | III D          | I C/(D) (? implant)    |
| 10      | I B                    | IV C           | 0                      |

*Grading at second evaluation. Vascular compression grading: Type I: Vertebral artery (VA); Type II: Posterior inferior cerebellar artery (PICA); Type III: Both VA and PICA; Type IV: Other; O: No artery adjacent to medulla; A: Artery proximate to medulla; B: Artery mildly compressing medulla; C: Artery moderately compressing medulla; D: Artery severely compressing medulla; MRI: Magnetic resonance imaging.
### Table 2: Good-fail A1c <7%

| Subject # | Preop. | 3-mo F/U | 6-mo F/U | 12-mo F/U | Last F/U | Mos last F/U | Difference |
|-----------|--------|----------|----------|-----------|----------|--------------|------------|
| 1         | 8.3    | 7.9      | 8.4      | 7.1       | 6.9      | 56           | 1.2        |
| 2         | 6.2    | 5.7      | 4.6      | 5.6       | 6.8      | 51           | 0.6        |
| 3         | 9.6    | 7.6      | 7.4      | 9.3       | 8.6      | 56           | 1          |
| 4         | 10.1   | 7.6      | 7.8      | 7.7       |          |              |            |
| 5         | 8.1    | 6.2      | 6.1      | 6.4       | 6.6      | 45           | 1.7        |
| 6         | 10.8   | 6.1      | 5.6      | 6.1       | 7.2      | 48           | 4.7        |
| 9         | 7.5    | 9.3      | 7.3      | 7.5       |          |              |            |
| Mean      | 8.657143 | 7.2      | 6.742857 | 7.1      | 7.22     | 51.2         | 1.657143   |
| Rnd mean  | 8.7    | 7.2      | 6.7      | 7.1       |          |              |            |
| Median    | 7.1    | 6.9      |          |           |          |              |            |

**Failed responders (n=3)**

| Subject # | Preop. | 3-mo F/U | 6-mo F/U | 12-mo F/U | Last F/U | Mos last F/U | Difference |
|-----------|--------|----------|----------|-----------|----------|--------------|------------|
| 7         | 7.4    | 7.0      | 7.8      | 8.5       |          |              |            |
| 8         | 7.5    | 8.5      | 7.9      | 11.0      | 8.4      | 48           |            |
| 10        | 10.6   | 12.1     | 12.5     | 13.3      |          |              |            |
| Mean      | 8.5    | 9.2      | 9.4      | 10.93333  | 8.4      | 48           |            |
| Rnd mean  | 8.5    | 9.2      | 9.4      | 10.9      | 8.4      | 48           |            |

**Total responders (n=10)**

**Mean**

- Preop.:
  - Good responders: 8.61
  - Failed responders: 8.5
  - Total responders: 8.61

- 3-mo F/U:
  - Good responders: 7.8
  - Failed responders: 7.8
  - Total responders: 7.8

- 6-mo F/U:
  - Good responders: 7.54
  - Failed responders: 7.54
  - Total responders: 7.54

- 12-mo F/U:
  - Good responders: 8.25
  - Failed responders: 8.25

- Last F/U:
  - Good responders: 8.25
  - Failed responders: 8.25

- Mos last F/U:
  - Good responders: 52.2
  - Failed responders: 46.5

### Table 3: Fasting blood glucose

| Subject # | Preop. | 12-mo F/U | Last F/U | Mos last F/U |
|-----------|--------|-----------|----------|--------------|
| #1        | 132    | 146       | 116      | 56           |
| #2        | 228    | 175       | 158      | 55           |
| #3        | 196    | 242       | 170      | 57           |
| #4        | 173    | 148       |          |              |
| #5        | 220    | 162       | 129      | 45           |
| #6        | 190    | 110       | 137      | 48           |
| #9        | 138    | 124       |          |              |
| Mean      | 182.4286 | 158.1429 | 142      | 52.2         |
| Rnd mean  | 182    | 158       |          |              |
| Median    | 190    | 148       | 137      |              |

**Failed responders (n=3)**

| Subject # | Preop. | 12-mo F/U | Last F/U | Mos last F/U |
|-----------|--------|-----------|----------|--------------|
| #7        | 155    | 210       |          |              |
| #8        | 154    | 259       | 141      | 48           |
| #10       | 308    | 273       | 187      | 45           |
| Mean      | 205.6667 | 247.3333 | 164      | 46.5         |
| Rnd mean  | 206    | 247       |          |              |

**Total responders (n=10)**

**Mean**

- Preop.:
  - Good responders: 189.4
  - Failed responders: 205.6667
  - Total responders: 189.4

- 12-mo F/U:
  - Good responders: 184.9
  - Failed responders: 247
  - Total responders: 184.9

- Last F/U:
  - Good responders: 185
  - Failed responders: 185

- Mos last F/U:
  - Good responders: 50.6
  - Failed responders: 50.6

**Total responders (n=7)**

**Mean**

- Preop.:
  - 148.3
  - Rnd mean: 148

- 12-mo F/U:
  - 184.9
  - Rnd mean: 185

- Last F/U:
  - 185
  - Rnd mean: 185

- Mos last F/U:
  - 50.6
  - Rnd mean: 50.6
Fasting blood glucose levels are collated in Table 3. In the group of good responders to MVD (7 patients), the median fasting blood glucose dropped from 190 preoperatively to 148 at 1 year. In the group of failed responders (3 patients), the median fasting glucose rose from 206 to 247.

Two-hour postprandial glucose (PPG) levels are collated in Table 4. The preoperative 2-hour PPG had only a modest decrease postoperatively in the group of good responders. The group of failed responders showed a severe increase (without medicine) at 12 months, implying progression of the diabetes.

Fasting serum insulin levels are collated in Table 5. The data show significant decrease in the group of good responders at 12 months. The serum insulin was also decreased in the group of failed responders. The reason for this improvement in patients who otherwise deteriorated is unclear. Perhaps there was a salubrious effect of the MVD even though the other parameters were indicative of failure.

Table 4: Two-hour postprandial glucose

|                 | Good responders (n=7) | Failed responders (n=3) | Total responders (n=10) |
|-----------------|-----------------------|-------------------------|------------------------|
| 2-hr PP         | w/med Preop. 3-mo w/med F/U 6-mo w/med F/U 2-hr PP no med Preop. 12-mo no med F/U |
|                 | #1 | #1 | #1 | #2 | #2 | #2 | #3 | #3 | #3 | #4 | #4 | #4 | #5 | #5 | #5 | #6 | #6 | #6 | #7 | #7 | #7 | #8 | #8 | #8 | #9 | #9 | #9 | Mean | Mean | Mean | Mean | Mean | Rnd mean | Rnd mean | Rnd mean | Rnd mean |
| #1              | 273 | 314 | 285 |
| #2              | 268 | 293 | 255 |
| #3              | 293 | 281 | 356 | 380 |
| #4              | 313 | 402 | 287 | 311 |
| #5              | 295 | 279 | 323 | 300.5 |
| #6              | 251 | 258.5 | 271.5 | 228.5 |
| #7              | 329 | 277.1667 | 291.4286 | 334.4286 | 291.5 |
| Total          | 329 | 277 | 291 | 334 | 292 |
| Mean           | 329 | 277 | 291 | 334 | 292 |
| Rnd mean       | 329 | 277 | 291 | 334 | 292 |
| Failed responders (n=3) | 2-hr PP |
| #7              | 280.5 | 296.5 | 276.5 | 147.5 | 363.5 |
| #8              | 330.5 | 311.5 | 279.5 | 350.5 | 478.5 |
| #10             | 443 | 453 | 458 | 466.5 | 460.5 |
| Mean            | 351.3333 | 353.6667 | 338 | 321.5 | 434.1667 |
| Rnd mean        | 351 | 354 | 338 | 322 | 434 |
| Total responders (n=10) |
| Mean            | 338.5714 | 302.6667 | 305.4 | 330.55 | 334.3 |
| Rnd mean        | 339 | 303 | 305 | 331 | 334 |

Table 5: Serum insulin

|                | Good responders (n=7) | Failed responders (n=3) |
|----------------|-----------------------|-------------------------|
|                | Preop. 3-mo F/U 6-mo F/U 12-mo F/U |
| #1             | 26.7 | 21 | 25 |
| #2             | 23 | 28 | 23 |
| #3             | 9 | 8 |
| #4             | 5.6 | 15 | 23 | 6 |
| #5             | 14 | 10 | 13 | 5 |
| #6             | 8 | 10 | 2 |
| #9             | 19 | 16 | 14 | 7 |
| Mean           | 16.3 | 14.6 | 17.3 | 8.6 |
| Rnd mean       | 16.3 | 14.6 | 17.3 | 9 |
| Failed responders (n=3) |
| #7             | 20 | 26 | 11 |
| #8             | 10 | 9 |
| #10            | 16 | 11 |
| Mean           | 16 | 13.66667 | 26 | 10 |
| Rnd mean       | 16 | 13.7 | 26 | 10 |

Fasting blood glucose levels are collated in Table 3. In the group of good responders to MVD (7 patients), the median fasting blood glucose dropped from 190 preoperatively to 148 at 1 year. In the group of failed responders (3 patients), the median fasting glucose rose from 206 to 247.

Two-hour postprandial glucose (PPG) levels are collated in Table 4. The preoperative 2-hour PPG had only a modest decrease postoperatively in the group of good responders. The group of failed responders showed a severe increase (without medicine) at 12 months, implying progression of the diabetes.

Fasting serum insulin levels are collated in Table 5. The data show significant decrease in the group of good responders at 12 months. The serum insulin was also decreased in the group of failed responders. The reason for this improvement in patients who otherwise deteriorated is unclear. Perhaps there was a salubrious effect of the MVD even though the other parameters were indicative of failure.

**Body mass index**

Baseline BMI of responders was 27.9 ± 2.1 SD, while that of nonresponders was 34.4 ± 2.5 SD. There was little-to-no change of BMI in the participants at 12 months postoperatively.

**CONCLUSION**

Of most significance is the finding that the normal course of disease progression was slowed in the majority of the participants. The reduction of diabetes medicines is also significant because of the decrease of the side effects associated with these medications that the patients may have to deal with. It is important to note that these improvements were seen while subjects made no behavioral changes, i.e., no weight change, no
changes in diet or exercise/activity levels. In clinical settings, life behavior changes of diet and exercise would be recommended and encouraged as is the standard of care. Body mass index appears to be an important factor in the outcome of this study. Those who had the best outcome from the intervention had BMIs identified as ‘overweight,’ while those who did not respond had BMIs in the obese category, viz., 30 or greater. The significance of this autonomic/metabolic abnormality spreads beyond type 2 DM. The implications are made with some surety that a number of problems of aging are due to arterial compression of the brainstem, specifically the medulla oblongata. The first of these problems is so-called essential hypertension, well known to neurosurgeons but with only early penetration into the general medical literature.

Many studies have been performed in attempts to show a genetic contribution in the inheritance of hypertension and diabetes. None of these have ever been able to complete the syllogism. It appears to us that one does not inherit hypertension. One does not inherit diabetes. Rather, one inherits blood vessels: veins and, especially, arteries. We inherit the size, the location, the proclivity for deterioration and elongation of arteries. We may possibly inherit the sensitivity of our myelin to pulsatile vascular compression.

As the senior author worked his way through the entities described above, caused by vascular compression of the cranial nerves and the brainstem, he found in the literature that many investigators had confused mechanism with etiology. The many excellent studies done on mechanism in diabetes are not mutually exclusive from the etiologic factors found here; rather they are complementary to this work.

Type 2 diabetes mellitus is associated with arterial pulsatile compression of the right anterolateral medulla oblongata, which appears to be an important etiologic factor. This etiologic factor must not be confused with mechanism. Instead, the many studies of the mechanism of type 2 DM correlate with, and complement this, etiologic process. Microvascular decompression may be an effective treatment for non-obese type 2 diabetes patients.

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