Parkinson's disease: an inquiry into the etiology and treatment

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Abstract

Parkinson's disease affects over one million people in the United States. Although there have been remarkable advances in uncovering the pathogenesis of this disabling disorder, the etiology is speculative. Medical treatment and operative procedures provide symptomatic relief only. Compression of the cerebral peduncle of the midbrain by the posterior cerebral artery in a patient with Parkinson's Disease (Parkinson's Disease) was noted on magnetic resonance imaging (MRI) scan and at operation in a patient with trigeminal neuralgia. Following the vascular decompression of the trigeminal nerve, the midbrain was decompressed by mobilizing and repositioning the posterior cerebral artery The patient's Parkinson's signs disappeared over a 48-hour period. They returned 18 months later with contralateral peduncle compression. A blinded evaluation of MRI scans of Parkinson's patients and controls was performed. MRI scans in 20 Parkinson's patients and 20 age and sex matched controls were evaluated in blinded fashion looking for the presence and degree of arterial compression of the cerebral peduncle. The MRI study showed that 73.7 percent of Parkinson's Disease patients had visible arterial compression of the cerebral peduncle. This was seen in only 10 percent of control patients (two patients, one of whom subsequently developed Parkinson's Disease); thus 5 percent. Vascular compression of the cerebral peduncle by the posterior cerebral artery may be associated with Parkinson's Disease in some patients. Microvascular decompression of that artery away from the peduncle may be considered for treatment of Parkinson's Disease in some patients.

Introduction

The pathogenesis of Parkinson's Disease is unclear.[1,2] The loss of pigmented neurons in substantia nigra, locus ceruleus, and brainstem nuclei is found in most forms of Parkinson's Disease. Depletion of the neurotransmitter substance Dopamine has been demonstrated in experimental animals and in humans. Etiologic mechanisms have been attributed to MPTP exposure, environmental neurotoxins, trauma, endogenous neurotoxins, genetic predisposition and genetic associations with a variety of mutations, oxidative stress and apoptosis. By clinical observation, one of us (PJ) noted magnetic resonance imaging (MRI) compression of the cerebral peduncle by the posterior cerebral artery on MRI scan in a patient with Parkinson's Disease and treated it. This encouraged us to perform a blinded study of MRI scans in age and sex matched Parkinson disease cases and control patients.

Materials and Methods

A 60-year-old woman had intractable left sided trigeminal neuralgia. She also had well-documented Parkinson's Disease. After microvascular decompression (MVD) of the left trigeminal nerve, MVD of the left anterolateral midbrain was performed. Based upon the MRI and intraoperative findings in the above patient, a blinded MRI study of 40 MRI scans, 20 with known Parkinson's Disease and 20 controls, was performed under the purview of an IRB approved protocol. Twenty MRI scans in patients with Parkinson's Disease and 20 age and sex matched control MRI scans were evaluated in a blinded randomized fashion by two groups of two investigators (PJ/DW and MF/RW). The Parkinson's Disease patients had been seen and followed in our Parkinson's Disease clinic with the diagnosis well established by clinical criteria. The study was approved by our IRB. The T2 study of the midbrain was evaluated in all patients. The T2 axial views of the midbrain were independently evaluated and interviewer discrepancies (only two in number) were aligned. Arterial compression-distortion of the cerebral peduncles was graded as follows: grade 0, no compression; grade 1, compression only; grade 2, compression and distortion of the midbrain. The offending artery was the posterior cerebral artery in every case.

Case Report

A 60-year-old woman was seen in the Jannetta Cranial Nerve Center, Department of Neurosurgery, Allegheny General Hospital, with the chief complaint of left facial pain of 11 years duration, which was lancinating, intermittent, and located in the left V3 distribution. This pain was exacerbated by the usual factors. The diagnosis of trigeminal neuralgia was made. She had taken increasing doses of phenytoin, baclofen, gabapentin, and carbamazepine, all of which had to be discontinued because of a lack of relief or side effects. Past medical history showed type 2 diabetes, and one transient ischemic attack. The diagnosis of Parkinson's Disease had been established 2 years prior to admission based on progressively severe resting tremor of the upper extremities, mask-like facies, postural instability, and cogwheel rigidity. The family history was non-contributory. Her medications included metformin for the DM2, carbamazepine for facial pain and amantadine for parkinsonism in a dose of 100 mg. b.i.d. She had been on carbidopa-levodopa to which she became intolerant. She was seen in consultation regarding operative treatment of her intractable trigeminal neuralgia. Physical examination showed a 60-year-old woman who had a prominent stare, mask-like facies, cog-

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Key words: Parkinson's disease, microvascular decompression, contralateral lateral peduncle, vascular compression.

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wheel rigidity of the upper extremities and an intermittent *pill rolling* type of tremor of the upper extremities. Her posture was stooped and gait showed small, uncertain steps with a tendency for festination. Neurological examination was otherwise normal. Specifically, the corneal reflexes, both upper and lower, were brisk and equal. Sensory and motor examination of the trigeminal nerve was normal. The diagnoses included: i) Intractable trigeminal neuralgia in the left V3 distribution; ii) Parkinson's Disease treated with amantadine; iii) Type 2 diabetes mellitus treated with metformin.

Special studies

Magnetic resonance imaging of the brain was reported as normal. One of us (PJ) noted that the left posterior cerebral artery was compressing and distorting the left cerebral peduncle (Figure 1). After discussion with the patient and her husband, it was decided to evaluate and treat the compression of the midbrain, if feasible, after microvascular decompression of the trigeminal nerve.

Operation

With the patient under general endotracheal anesthesia in the right lateral decubitus position a left retromastoid craniectomy and microvascular decompression of the trigeminal nerve was performed using techniques previously described.[3] The anterolateral midbrain was then exposed by angling the microscope rostrally. The posterior cerebral artery grooving the midbrain (Figure 2) was mobilized and held away with an implant of soft shredded Teflon felt (Figure 3). The wound was then closed in the usual manner.

Results

The postoperative course was benign. The patient awoke with the face pain relieved and without the mask-like facies. The cogwheeling rigidity was gone by the first postoperative day. There was no tremor at any time. She was discharged from the hospital on the second postoperative day. When seen on the fifth postoperative day, she was pain free and without signs of parkinsonism. She remained well for 18 months and then suffered recurrence. MRI scan now showed compression of the contralateral cerebral peduncle by the PCA (Figure 4).

Magnetic resonance imaging study

The MRI study was deemed inadequate in one Parkinson's Disease patient. Of the 19 Parkinson's Disease patients, 13 had clear compression-distortion of one or both of the cerebral peduncles by the posterior cerebral artery (78%). Four were bilateral. Seven were Grade 2. Of the 20 control patients, only 2 had compression of the cerebral peduncle, each with a Grade 1. One of these two patients was later diagnosed with Parkinson's Disease. Three patients had questionable compression. The other control scans showed no arterial compression-distortion of the peduncle. (Figure 5) These data are collated in Tables 1 and 2. Figure 6 shows bilateral compression in a Parkinson's Disease patient. Statistical

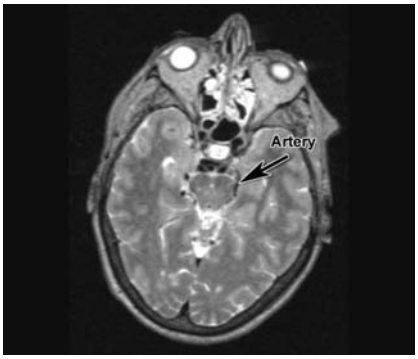

Figure 1. Magnetic resonance imaging scan T2 axial view at level of midbrain. Arrow points to area of compression of left cerebral peduncle by posterior cerebral artery. Clear space filled with cerebral fluid is seen on the right.

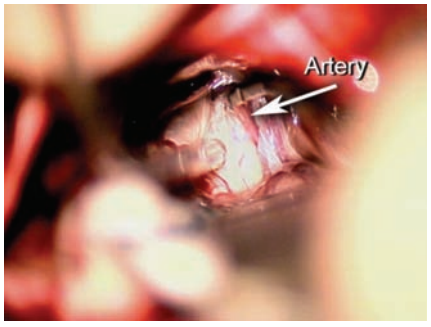

Figure 2. View through microscope of left cerebral peduncle in patient with Parkinson's Disease. Arrow points to PCA partly buried in the midbrain.

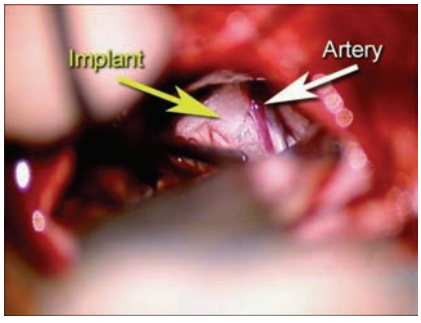

Figure 3. Same view as Figure 2. Artery has been mobilized away from the cerebral peduncle and decompressed using shredded PTFE felt.

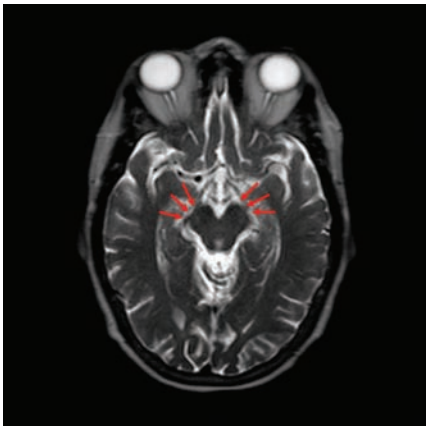

Figure 4. Magnetic resonance imaging T2 axial view two years postoperatively. Recurrence began about 18 months postoperatively. Left caudal peduncle shows implant separating PCA (three arrows). Right cerebral peduncle now compressed by PCA (two arrows).

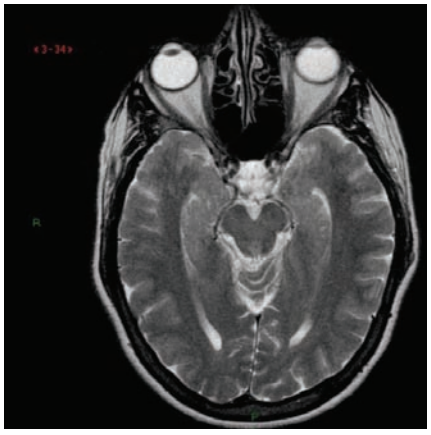

Figure 5. Magnetic resonance imaging T2 axial view at the level of midbrain in control patient without Parkinson Disease. Note that posterior cerebral arteries do not impinge upon cerebral peduncle. A clear space filled with cerebrospinal fluid is seen bilaterally.

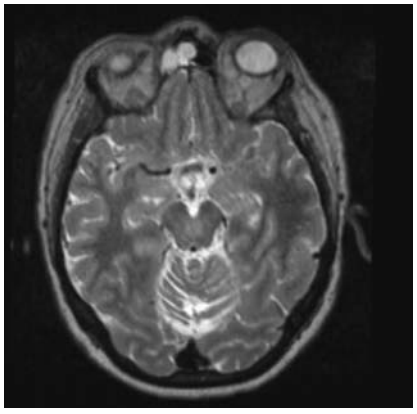

Figure 6. Magnetic resonance imaging T2 Axial view. Bilateral compression in patients with Parkinson Disease.

Table 1. Parkinson disease: compression of cerebral peduncle by posterior cerebral artery.

Parkinson Disease (Parkinson's disease) Group n=19					Arterial compression	Control group n=20				
ID #	Right	Left	Sex	Age	Grading Scale	ID #	Right	Left	Sex	Age
1	1 ?2	2	F	64	0 No Contact	2	0	0	M	56
4	0	2	F	67	1 Contact	3	0	0	M	58
6	?	1	M	57	2 Distortion	5	0	0	M	58
7	0	0	F	69	? Possible contact	8	0	0	M	59
9	0	0	M	59		11	0	0	M	61
10	?	0	M	71	Parkinson's disease female mean age	12	?	0	M	62
13	0	0	M	62	66.625	14	0	0	M	63
16	1	0	F	82		15	0	0	M	63
17	0	0	M	72	Parkinson's disease male mean age	19	0	0	M	64
18	0	1	M	62	61.727	20	0	0	M	70
21	1	0	F	81		22	?	0	F	57
23	0	1	M	59	Control female mean age	24	0	0	F	57
26	2	0	M	68	62.6	25	0	0	F	57
27	2	0	F	67		29	1	0	F	59
28	1	2	F	50	Control male mean age	30	0	0	F	59
31	?	1	M	50	61.4	33	?	0	F	63
32	1	2	F	53		34	0	0	F	66
35	2	1	M	59	Parkinson's disease & controls mean age	36	0	0	F	67
39	0	0	M	60	62.871	38	0	?	F	70
						40	1	1	F	71

Parkinson's disease patients vs. controls. Side, frequency, and degree (Grade) of arterial compression. 0 = No contact of artery on cerebral peduncle. 1 = Artery is touching cerebral peduncle. 2 = Artery is compressing cerebral peduncle to cause distortion. ? = Scan not clear enough to determine if artery touching cerebral peduncle or not.

analysis was performed utilizing MedCalc for PC 9.6.4.0. A forward logistic regression was performed with the diagnosis of Parkinson's Disease as the dependent variable and age, sex and maximum degree of vascular compression on either side as covariates.

There was a significant relationship between a diagnosis of Parkinson's Disease and maximal degree of radiographic vascular compression (P=.006), OR 9.0 (95% CI 1.9-43.1), with 78% of cases correctly classified. Although the overall distribution of extent of compression was nearly identical when comparing each side (Chi-square 1.63, P=.65) the correlation of degree of compression in each individual was low (kappa = .2).

Table 2. Parkinson's disease. data collated – parkinson's disease patients and control patients.

Grade	0	%	1 or 2	%	?	%
PD n=19	5	26.3	13	68.4	1	5.3
C n=20	14	70	2	10	4	20

Parkinson disease: arterial compression of Midbrain. Grading scale: 0 No Contact; 1 Contact; 2 Distortion; ? Possible Contact/Distortion. Note: one of 2 patients with compression subsequently developed Parkinson's disease.

Discussion

Beginning in 1966, a growing number of cranial nerve and brainstem syndromes have been reported to be caused by pulsatile vascular compression, arterial or venous or both. These include such apparently disparate problems as trigeminal neuralgia[3-5] (both typical and atypical), hemifacial spasm,[6,7] Meniere's disease,[8] disabling positional vertigo,[9] glossopharyngeal neuralgia,[10-12] Bell's palsy,[13] essential hypertension[14-17] and type 2 diabetes.[18,19] This knowledge of the above entities, although known and accepted in the neurosurgical community, have not penetrated into the general medicine literature. Beginning in the same year (1966), treatment of the pulsatile compression (microvascular decompression) was developed. These findings and treatments were possible because of the use of then new technology, and the magnification, lighting and recording capabilities of the surgical binocular microscope.[13-19]

It is estimated that over one million people in the United States have Parkinsonism from various causes. The incidence increases with advanced age, although it is known that young people may develop a rapidly advancing form of Parkinson's Disease. The true etiology of Parkinson's Disease has been unclear, but it is well recognized that loss of pigmented neurons, especially the substantia nigra, locus ceruleus, and brainstem nuclei is found in virtually all forms. Many careful investigators have stated that they do not know the etiology and have called Parkinson's Disease idiopathic, i.e., the true primary etiology is unknown. The loss of pigmented neurons is associated with the presence of Lewy bodies in the basal ganglia and upper brainstem. Pathogenic mechanisms have been related to MPTP exposure, environmental neurotoxins, trauma, the enigmatic neuroprotective effect of smoking, endogenous neurotoxins, and genetic factors.

One reason that arterial compression of the cerebral peduncle was never noted may be because of the technique of the standard post mortem examination of the brain. For the post mortem exam, the calvarium is removed with a power saw. The dura mater is removed. The forebrain is then raised up off the frontal-temporal fossa and the region of the midbrain transected using a scalpel or scissors. This, the area of the vascular compression, is unfortunately stretched, distorted and at times transected. Subtle neurovascular relationships are lost. The autopsy technique of removal of the hindbrain also has denied careful study of neurovascular relationships of the pons and medulla even if the brain has been removed in one piece. In any case, arterial relationships have generally been found by pathologists.

The pathophysiology of pulsatile compression of the cerebral peduncles may be the same as vascular compression of the cranial nerves and medulla oblongata. Severe compression of central nervous tissue causes rapid or severe loss of function. This is seen in Bells

palsy when a shifting artery, usually the anterior inferior cerebellar artery stretches and compresses the facial (and to a lesser degree) the auditory nerve.[13] Fortunately, this physically tough motor nerve usually (80 percent) recovers function in time. Modest and progressive pulsatile compression, on the other hand, causes hyperactive symptoms, a caricature of the normal function of the nerve, (i.e., sensation --- pain, motor function --- twitching and spasm). As it progresses, loss of function occurs, (i.e., numbness, weakness). ultrastructural changes of hypermyelination, hypomyelination, kissing axis cylinders, dead, dying and regenerating axis cylinders are seen spread over a background of normal axons and myelin.[20-22] The loss of substantia nigra cells and coloration may be a part of this process. This of course is a later stage of the disease seen at post mortem exam while the ultrastructural changes in the cranial nerves are from operative specimens. These changes reflect a dynamic and progressive process of hyperactivity and the loss of function. Ephaptic transmission and kindling may each play an important role.[23,24]

Medical and operative treatment consists of dopamine agonists and the replacement of MAO and COMT inhibition and operative intervention with brainstem lesions and stimulation.[25-27] In virtually all cases the disease progresses despite therapeutic intervention. Various studies including glial-derived nerve growth factor, and many medications and possible operative intervention are currently in process.

The present data raise questions regarding etiology which may be answered over time: i.e., Does unilateral cerebral peduncle arterial compression cause unilateral disease only? Can it cause bilateral Parkinson's Disease in time? Can MVD relieve parkinsonism? Is there a form of parkinsonism related to arterial compression of the cerebral peduncle? Is Parkinson's Disease in young people the same etiologically as in the older population? Are Cognitive changes reversible? Will MVD of the cerebral peduncle be as safe and effective as MVD is for other problems?

A multi center MRI trial has been organized for further evaluation of this concept. Microvascular decompression of the brainstem should be performed only by specially prepared neurosurgeons with a background in microvascular decompression and training by the senior author.

On the basis of these data, some cases of Parkinsonism may be associated with arterial compression of the cerebral peduncle by the posterior cerebral artery which may frequently be seen on MRI studies. Improvement and prolonged relief of Parkinson's Disease in one patient demonstrates that relief of Parkinson's Disease may be possible in certain circumstances.

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