The History of Surgery for Parkinson's Disease

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Introduction: from the streets of London

Although the manifestations of Parkinson's disease can be found described in numerous ancient writings, including Ayurvedic and Chinese medical texts from as early as 1000 BC (1,2), James Parkinson's foundational "Essay on the Shaking Palsy" in 1817 was the first modern medical description of the disease (3). In it, Parkinson reports on six individuals exhibiting signs and symptoms of the disease, displaying a Holmesian flair for observation, vivid description, and abductive reasoning. In fact, three of the six cases were not formal patients of his, but people he met casually during his walks through London – one was only observed from a distance. He summarized his findings succinctly (3):

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Parkinson describes with great accuracy and uncompromising detail, the natural progression of the disease and its impact on his patients, including its slow and insidious onset, the unilateral resting tremor of the arms, legs, or jaws, and its eventual progression to the point it interferes with writing and feeding. He describes the stooped posture, shuffling gait and propensity for falling, and even goes on to describe some of the non-motor manifestations of the disease, including disordered sleep, drooling, and constipation. So impressive were the seminal descriptions in Parkinson's monograph, that the great French neurologist Jean-Martin Charcot, who provided a more thorough account of the disease some fifty years afterwards, coined the eponymous term, "La maladie de Parkinson," after him (4).

Parkinson erroneously localized the pathology of this disease to the cervical spinal cord, given its effect on all four limbs, and his presumption that the senses and intellects were unaffected (3). He speculated that the pathology eventually spread to the medulla oblongata, where it affected swallowing and speech later in the disease (3). He proposed that bloodletting from the neck may help to relieve congestion in the cervical spinal cord, as a potential treatment for the disease (3). Although he did not attempt such a procedure on any of his patients, Parkinson's surgical empiricism is apparent in the 4th of his 6 cases in the Essay – a patient with a 5 year history of "trembling of the arms" who presents with a chest wall abscess. Parkinson drains the abscess and notes no improvement in the tremor afterward. He wonders if there was any connection and regrettably states that he was unable to follow up with the patient's progress as the patient subsequently moved to a distant part of the country (3). As a surgeon, Parkinson would have appreciated the variety of procedures, as well as the technical and theoretical advancements, which will be outlined here, developed for the treatment of the disease which bears his name.

First steps

At the end of the 19th century, much of the understanding of motor pathways was limited to peripheral mechanisms; fittingly, the first reported surgery aimed at treating parkinsonian motor symptoms was bilateral cervical posterior rhizotomy performed by the French surgeon René Leriche in 1912 (5). This operation, introduced by Otfrid Foerster in 1911 to treat spasticity in children with cerebral palsy, derived its motivation from Nobel Laureate Charles Sherrington's work on the role of propriospinal reflexes in rigidity in the decerebrate cats (6,7). Sherrington writes in his 1898 manuscript, "If after ablation of both cerebral hemispheres, even when the

rigidity is being maintained at its extreme height, the afferent roots are carefully severed, the limb at once falls into flaccidity" (7). Although Foerster had good results in his cerebral palsy patients, Leriche reported mixed results, with only slight improvement in arm function and some suppression of tremor (6). Other surgeons only achieved the slight relief of rigidity, with tremor unaffected, and some patients developed permanent flexion of the wrist, biceps, and neck, causing this procedure to fall out of favour (8). Other peripheral surgeries continued to be performed, however, largely due to an epidemic of a form of encephalitis known as encephalitis lethargica between 1916 to 1927 (9). This disease, first described by the neurologist von Economo, induced catatonia and parkinsonism in many of its patients, and neurectomies, sympathetic ramisectomies, and ganglionectomies were performed under the assumption that these neurologic structures were carrying residual infection, as the cause of the parkinsonism (9). The results were poor, however, and these procedures were abandoned.

Pyramidal tract procedures: surgery for compromise

It is interesting that procedures to the central nervous system did not occur sooner, given that it was well known that parkinsonian tremor was abolished with hemiplegia from strokes – Parkinson himself describes an episode of stroke and hemiplegia in his 6th case patient, which rids the patient of his tremor (3). Indeed, cortical ablation for a case of severe hemi-athetosis was performed by Victor Horsley with good result as early as 1908 (10). Cortical ablation for tremor, however, was not attempted until 1937, by Bucy and Case, who removed the pre-central cortex as well as the adjacent premotor cortex (11). It was successful in permanently alleviating the post-traumatic tremor, albeit at the expense of neurologic motor deficit. These ablations also induced hyperreflexia, clonus, dyspraxia, and impairment of fine limb movements, and was only

performed if this was a more acceptable deficit than the tremor. Other complications, such as post-operative mortality (17%), epilepsy, and lack of improvement of bradykinesia and rigidity precluded widespread uptake of this technique (12).

Other surgeries targeting the pyramidal tract included Putnam's high cervical lateral pyramidotomy in 1940 (13). It reduced tremor and rigidity with less motor function impairment than cortical ablation. More than half his patients had satisfactory reduction of tremor, and importantly, none died (13). Other surgeons, including Ebin and Oliver attempted to modify the technique to further reduce tremor; however, the benefits were still not consistent and complications included contralateral anesthesia and loss of sexual function (14,15). Arthur Walker attempted to find a site to interrupt the corticospinal tract with minimal danger of injuring other structures, and performed the mesencephalic pedunculotomy in 1949 (16). Guiot and Pecker, among others, performed variations of this procedure, and found that tremor relief was proportional to the severity of hemiparesis (17).

Venturing where none dare: extrapyramidal territory

In 1939, Meyers first performed deliberate surgery on the basal ganglia with good result, in a woman with left sided tremor due to post-encephalitic parkinsonism (18). Until then, surgeries on the basal ganglia were avoided, given Walter Dandy's assertion that injuries to the basal ganglia would result in alteration of consciousness (19). Meyers was subsequently unable to reproduce his initial favourable outcome by ablating the head of the caudate, and as such started a series of experimental surgeries, by making various combinations of surgical lesions in a systematic way (17). His operations were performed under local anesthetic to allow for clinical

monitoring, and he used a transcortical, transventricular approach to remove portions of the basal ganglia (17). He found that cutting the pallidofugal efferent pathways produced the best results for parkinsonian tremor and went on to perform many of these surgeries, with 60% of his patients improved or much improved after surgery and mortality rate dropping to 10% (17). Ultimately, Meyers felt that the mortality rate of 10% was too high for an elective procedure, and that his surgery of the basal ganglia had a limited role to play in the treatment of Parkinson's disease. He did demonstrate, however, that surgery of the basal ganglia does not cause disturbance of consciousness and that it could ameliorate tremor and rigidity without the hemiplegia of the pyramidal tract procedures (17).

In 1952, Irving Cooper inadvertently tore the anterior choroidal artery during a pedunculotomy for a patient with post-encephalitic parkinsonism and was forced to ligate the vessel (20). To Cooper's pleasant surprise, following emergence from anesthesia, the patient's tremor and rigidity were abolished without any residual hemiparesis. He went on to perform anterior choroidal artery ligation in 55 patients with parkinsonism, eliminating tremor in nearly 65% and decreasing rigidity in 75% at the cost of 11% of patients suffering hemiplegia and 10% operative mortality (20). Although anatomic studies demonstrated that the anterior choroidal artery supplied many structures within the basal ganglia (globus pallidus, subthalamic nucleus, ansa lenticularis), as well as the hippocampus, ventrolateral thalamaus, red nucleus, optic tract, lateral geniculate body, and posterior limb of the internal capsule, the variability of clinical effect in ligating the artery itself limited its usage by other surgeons (17). However, Cooper's serendipitous observation, together with Meyer's earlier work, helped focus surgical efforts on

targets within the basal ganglia and, later, within the thalamus to alleviate the movement disorders associated with Parkinson's disease (17).

A neurosurgical revolution: the stereotactic era

Around this time, a technical revolution was taking place in the young field of neurological surgery – in 1947, with their road paved by the previous work of Horsley and Clarke on animal stereotaxy, Spiegel and Wycis developed the first human stereotactic device (21). They utilized pneumoencephalograms and contrast ventriculography to visualize intracranial landmarks around which a three-dimensional Cartesian coordinate system could be constructed to guide surgeries. In 1952 they published the first human stereotactic atlas, which greatly reduced operative mortality – a mere 2.0% compared to the above mentioned open procedures (21). This monumental development essentially allowed for the development of modern functional neurosurgical procedures. In a short period of time, several other groups had developed their own stereotactic devices and began to perform stereotactic pallidotomies.

None of the groups had consistent, excellent results with the pallidotomies, and so began to experiment. Hassler and Riechert in Freiburg performed detailed retrograde tracing studies and characterized pallidothalamic and thalamocortical projections that ultimately led him to the more satisfactory ventral intermediate nucleus of the thalamus as a target to reduce tremor (21). Cooper had a more serendipitous course to the same conclusion, when a pallidotomy patient of his with a particularly good tremor resolution passed away, and the autopsy demonstrated the lesion had been off its mark – and in the ventrolateral thalamus instead (21). Leksell in Sweden in the late 1950’s continued to perform pallidotomies, but systematically varied lesion location

and analyzed the clinical outcomes, finding the optimal location for reduction of tremor and rigidity to be in the ventral posterior pallidum (22). Unfortunately, this work did not draw much attention as many had already turned their attention to the thalamus and Hassler's work.

The death and rebirth of surgery for Parkinson's disease: the advent of levodopa

Stereotactic surgery, still in its infancy, became an outdated treatment modality for parkinsonism in 1969, with the advent of levodopa through a monumental clinical and translational medicine effort, led by George Cotzias and Arvid Carlsson. Carlsson's work in the 1950's demonstrated that pharmacological depletion of dopamine in animal models produced movement disorders similar to Parkinson's, and Cotzias et al. eventually developed levodopa for the treatment of parkinsonian symptoms (23). Given the clinical efficacy, and the less invasive nature of levodopa, the performance of stereotactic surgeries for parkinsonism declined dramatically almost overnight (21). It was not until a few years later, beginning in the mid 1970's that the shortcomings of levodopa therapy were recognized: it did not prevent progression of the disease, some tremors were refractory to medication, and long-term use produced significant side effects and dyskinesias (21). This led to the rebirth of ventrolateral thalamic surgery for medication-resistant tremor, as well as Laitinen's rediscovery in 1985 of Leksell's posteroventral globus pallidus (GPi) target – today's target of choice for rigidity and levodopa-induced dyskinesias (24).

The surgical treatment of Parkinson's disease has seen a renaissance since the mid 1970's that has continued to thrive with the development and application of deep brain stimulation (DBS) of Parkinson's targets (24). Chronic stimulation of the subthalamic nucleus was shown to be

effective in relieving all of the cardinal movement abnormalities in Parkinson's patients (bradykinesia, tremor, and rigidity) (25). Though the mechanisms of DBS remain to be fully elucidated even today, its clinical application as a modifiable, "reversible lesion" has made it the modality of choice in today's surgeries for Parkinson's disease. Recent literature supports the use of DBS even earlier on in the course of disease in appropriate candidates, to maximize benefit and quality of life for patients (26).

Concluding remarks and future directions

Having taken some time to look back at the history of this disease, it is interesting to note that no image or portrait of James Parkinson survives today. A Google image search of the name curiously brings up a single photograph of a stern, bearded man that has been mistakenly and unfortunately inescapably attached to his name, since Parkinson passed away from a stroke in 1824 – two years before the invention of photography (27). Today, Parkinson's disease has many faces. Particular spotlight is given to celebrities like Michael J. Fox and Muhammad Ali, but it is a disease that is now common enough and well known enough that most people will know a friend or family member afflicted with the condition.

The recent research in Parkinson's disease implicates the irregular aggregation of proteins known as α-synuclein into Lewy Bodies as a putative etiology of the disease and emphasizes that it involves the entire body, not just motor circuits (28). Current research objectives focus on methods of identifying an at-risk pre-clinical population, the so-called "Parkinson's at-risk syndrome" (PARS) (28). Once identified, the goal would be to conduct prospective studies on this cohort in order to ascertain therapies that prevent the progression of disease (28). As

Parkinson astutely observed in his monograph, the key to defeating this disease lies in discovering treatments “by which, at least, the progress of the disease may be stopped” (3). Until then, neurosurgical procedures will continue to play an important role in the multi-modal treatment of carefully selected patients with Parkinson’s disease.

Although surgical interventions for Parkinson’s disease have been instrumental to our understanding of the disease and of the nervous system, and comprise a story steeped in innovation, tenacity, and serendipity, we continue to hope and strive to see the day when we no longer will have to depend on the scalpel to treat this disease, and the history of surgery for Parkinson’s disease will be just that – history.

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