Movement Disorders
CLINICAL PRACTICE
IN FOCUS
HISTORICAL REVIEW

Svennilson's Publication on Pallidotomy for Parkinsonism in 1960: A Most Influential Paper in the Field

Svennilson E, Torvik A, Lowe R, Leksell L. *Treatment of parkinsonism by stereotactic thermolesions in the pallidal region. A clinical evaluation of 81 cases*. Acta Psychiatr Scand 1960;35(3):358–377.

When *Treatment of parkinsonism by stereotactic thermolesions in the pallidal region* was published in *Acta Psychiatrica Scandinavica* in 1960 by *Svennilson, Torvik, Lowe and Leksell* it received only little if any attention.[1] At that time, thalamotomy had replaced pallidotomy in most stereotactic surgery centers for several reasons as outlined below.[2,3] Svennilson's manuscript with its interdisciplinary approach, its meticulous analysis and its careful interpretation of data soon fell into oblivion for the next decades to come. It became clear only in hindsight that it was one of the most important papers in functional neurosurgery for treatment of parkinsonism when the renaissance of pallidal surgery was heralded by Laitinen's rediscovery of pallidotomy in the early 1990s.[4]

In their paper published in 1992 *Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease* the authors *Laitinen, Bergenheim and Hariz* explicitly mentioned that they were inspired to reconsider pallidotomy regarding statements by Leksell in verbal discussions and by their appraisal of Svennilson's manuscript.[4] They concluded that they were able to confirm the findings of Svennilson showing a long-lasting effect on parkinsonian symptoms after "Leksell's pallidotomy". While it is unknown how many citations Svennilson's manuscript received after its publication in 1960 with regard to the lack of bibliographic metrics at that time, Laitinen's manuscript published in 1992 became a citation classic with 883 citations in Scopus at the writing of this viewpoint and a mean of 29.52 citations per yearbecoming also a most influential and seminal paper by itself.[5]

Even nowadays in the time of large medical databases Svennilson's original manuscript is difficult to obtain without having to pay a fee for its access. In the following we will first summarize the most remarkable findings of this manuscript and then concentrate on some particular issues.

Svennilson's Manuscript

The manuscript was published in a Scandinavian journal which is still active nowadays. It had 19 pages and it was accompanied by eight figures, and three of these figures showed individual outcomes of rigidity and tremor.

The series of Svennilson and Leksell, and co-workers comprised 81 parkinsonian patients operated between 1953 and 1957 in Lund, Sweden. The study design was prospective and patients were followed up for at least 1 year after surgery with the earliest patients of the series having follow-up for 5 years.

Age at surgery ranged between 30 to 75 years, and 65% of patients were over age 50. While parkinsonism was predominantly unilateral in 54%, advanced bilateral disease was present in 30%. Exclusion criteria for surgery were recent disease onset, mild disability, tremor as the main clinical symptom, advanced age or severe cerebral atrophy. Pallidal lesions were made stereotactically with a special electrode set consisting of a pair of electrodes set 8 mm apart with the lesion temperature being controlled by a thermoelement (Fig. 1A). While most patients had unilateral pallidotomies, three had bilateral surgery. The target within the pallidum as well as lesion parameters were varied during the 4-year period of the study. It appeared that the best results were achieved when the lesion was placed on the "postero-medial aspect of the medial nucleus of the pallidum, just anterior to the internal capsule and 20 mm from the midline" (the region we actually now refer to as the posteroventral lateral globus pallidus internus (GPi)).

Parkinsonism was secondary to various etiologies and the authors stressed that they noted "a history of illness resembling an encephalitis in less than 20 per cent of the cases". Brain atrophy was assessed by air encephalography which was the standard cerebral imaging method at that time. The authors were aware of the limitations of this approach when they explained that the size of the anterior horns of the lateral ventricles was used as "some measure, however crude", to determine the presence or absence of atrophy. Certainly, one of the unique features of this study was the assessment of the patients' clinical symptoms: "Each patient was examined by two observers working independently". Rigidity and tremor were assessed for each limb and graded according to numerical

***Correspondence to:** Prof. Dr. Joachim K. Krauss, Department of Neurosurgery, Medical School Hannover, MHH, Carl- Neuberg- Straße 1, 30625 Hannover, Germany; E-mail: krauss.joachim@mh-hannover.de
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scores. Mean values of the scores obtained from the two examiners were obtained preoperatively and at follow-ups ranging from 1 to 5 years.

While relief of rigidity and tremor was noted in 79% and 82% of patients, respectively, improvement of both rigidity and tremor was seen in 77% . Remarkably, the figures accompanying the manuscript showed data of the individual assessment of all patients for rigidity and tremor (Fig. 1B). Marked effects in the "degree of incapacity" occurred in about 2/3 of patients (Fig. 1C). The authors stressed that 25% of patients who were unemployed prior to surgery resumed work. While 37% of those who required assistance preoperatively became independent, 66% of patients who were unable to fend for themselves were able to resume useful activities later on. Positive effects were also seen in depression, "painful muscular spasms and intermittent cramps", and gait. While there was no postoperative mortality and no visual field defects were reported, 54% of patients had "a transitory pyramidal or facial lesion", and three patients had "a more extensive paresis". The operation had little effect on dysarthria, but transient "dysphasia" was noted in 24% of patients with wide ventricles, and in 7.5% of those with normal ventricles when surgery was performed on the dominant hemisphere. Psychiatric and cognitive changes were more frequent in those with cerebral atrophy. Both improvement of tremor and rigidity was seen in 95% of patients in the subgroup in whom the posteroventral lateral GPi had been targeted.

Bradykinesia was neither rated separately nor assessed by a numerical score, but the authors outlined under the heading *General function* that "the most obvious gain was improved mobility, in terms of strength, range, speed, and precision". They also noted that this improvement paralleled the amelioration of rigidity concerning mainly the contralateral limbs. Most remarkably the authors stated in the discussion "Tremor, hypokinesia, and rigidity are relieved to an equal extent by operation".

While the study did not explicitly outline the development of parkinsonian symptoms in the postoperative course at different time points, the authors noted that both tremor and rigidity became worse again in several instances. The authors rather attributed recurrence of symptoms to "insufficient" lesions than to the natural course of the disease. They even stated that they did not find "evidence of progressive recurrence at a later stage even in patients whose ability was advancing on the opposite side of the body."

Discussion

The manuscript of Svennilson and colleagues was well ahead of its time when it was published in 1960.[2,3,6,7] Although several previous studies had shown beneficial effects of pallidotomy none had included such an astute description of both the postoperative changes of symptoms and the mostly transient side effects.[2,6,8]

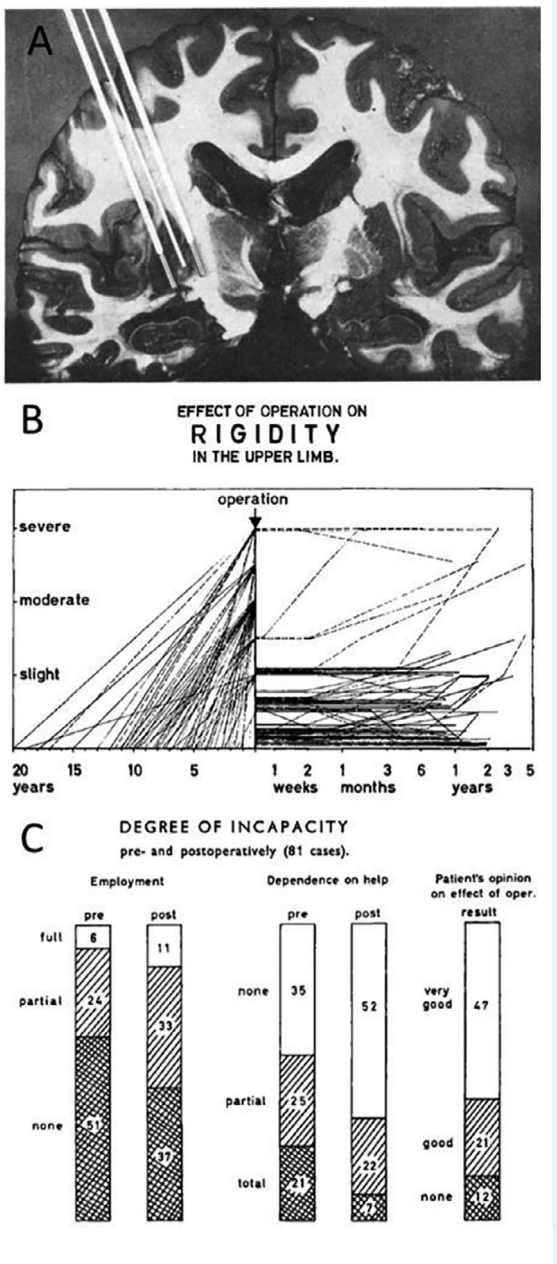

FIG. 1. Svennilson's publication on pallidotomy for parkinsonism in 1960. (**A**) Coronal section of normal brain in region of pallidum. Section placed after ventriculography in same plane as lesions in operated series. Left: Electrodes in position with thermoelement in the middle. (**B**) Effect of operation on rigidity in the upper limb. Diagram of degree of rigidity before and after operation. Each case is represented by one line. The different levels indicate the severity of the rigidity. To left: Duration of symptoms before operation (linear scale). To right: Rigidity after operation (log. scale). Interrupted lines indicate unsuccessful cases. On this diagram are recorded the 61 first cases: the following 20 have shown about the same tendency. (**C**) Degree of incapacity pre- and postoperatively (81 cases). General functional ability before and after operation (left) and patient's opinion of the value of the operation (right). Values in brackets indicate number of patients in each group. Figures and legends *with permission* from the original publication.[1]

The pallidum had been introduced as a surgical target by Meyers already in the 1940s,[9] but only after the introduction of stereotactic surgery by Spiegel and Wycis in 1947—originally designed for treatment of psychiatric disorders[10]—it was more widely appreciated for the treatment of parkinsonism. Probably the first stereotactic pallidotomy was performed in 1948 in a patient who suffered from Huntington's disease providing relief for contralateral chorea.[11] Narabayashi performed his first pallidotomies for parkinsonism in Japan as early as in 1951 (personal communication, JKK) and other experiences were soon published by different groups worldwide.[6,12,13] During the 1950s the pallidum had become the main target for movement disorders surgery and several studies reported on techniques and clinical outcome.[2,3] One major problem was the heterogeneity of parkinsonian syndromes at a time when postencephalitic parkinsonism was common and the concept of "atypical parkinsonian syndromes" had not been formulated yet. Overall, abolition or reduction of rigidity was described in 50% to 90% in different series, and improvement of tremor in about 45% to 85%.[2,3]

Although Svennilson and colleagues did not investigate the effect of pallidotomy on bradykinesia in such detail as for tremor and rigidity, they were probably the first to give clearly outspoken comments on the improvement of hypokinetic symptoms. While it had been occasionally noted before that bradykinesia was ameliorated by pallidotomy, there was no theoretical framework at all which would have provided rationales to explain such a phenomenon. First of all—as opposed to rigidity—bradykinesia was not considered to be related directly to basal ganglia dysfunction by many investigators, but rather to impaired "conduction from the nigra cells to the anterior horn motor apparatus".[14] Second, it could not be understood that a "negative motor symptom" such as bradykinesia would be improved by a lesion. But even those, who acknowledged that bradykinesia was improved sometimes, thought that this effect was due to "the relaxation of the muscular hypertonia" that is secondary to the relief of rigidity.[15] The scenario at that time and also in the years thereafter concerning bradykinesia was nicely resumed by Hassler in his statement "for theoretical reasons alone, one could hardly expect an improvement of akinesia by a stereotaxic operation".[14]

Another aspect that deserves special consideration in Svennilson's study is the choice of the pallidal target.[16] There was little consensus in the 1950s where the lesion would be best placed in the pallidum and also whether pallidotomy should be complimented by pallidofugal fiber tract lesioning. In 1959, Levy published a comparative study on the pallidal target used by different groups in the treatment of parkinsonism.[17] The pallidal targets were depicted graphically and the wide variations were demonstrated including targets in the anterior and medial GPi, the globus pallidus externus, combined regions, and in few exceptions the "modern" posteroventral lateral GPi. Again, however, it was the merit of Leksell's group to link this target to improvement of bradykinesia.[1]

One of the major reasons which impeded comparison of the results of pallidotomy in the pre-levodopa era was the lack of commonly accepted and standardized assessment of the symptoms and the severity of parkinsonism.[2,6] Often the effects of surgery were described just as "improved" or "abolished", but even when more elaborated rating scales were used it was unusual at that time to evaluate functional disability and quality of life. It must be kept in mind that the more common rating scales for parkinsonism from Schwab and England, Webster, and Hoehn and Yahr gained wider popularity only during the late 1960s. Furthermore, interdisciplinary collaboration with "independent" assessment such as performed by Leksell and Svennilson was quite unusual during the 1950s. Also, reporting of individual patient outcome data in addition to that of mean values is a striking feature of this report.

The eclipse of pallidotomy occurred in the late 1950s. At that time there were also some other neurosurgeons apart from Leksell who had advocated to adopt a more posterior and inferior target in the GPi, but this target region did not gain wider acceptance then.[2,17] Certainly, the most important reason for the abandonment of pallidotomy was the ever rising popularity of thalamotomy.[6,7,18] Based on his neuroanatomical work on the thalamus Hassler had reasoned that regions in the ventrolateral thalamus would be the optimal target for the relief of tremor.[19] Following his line of thoughts, the first thalamotomy for treatment of parkinsonian tremor was then performed in Freiburg in 1952, and the results demonstrating the abolition of tremor were published in 1954 in *Der Nervenarzt*.[20] Several studies thereafter showed improvement of both tremor and rigidity and the thalamic target slowly replaced pallidal lesioning in the late 1950s worldwide for treatment of parkinsonism.[2,3,6] It was only a few years later, however, that the introduction of dopamine replacement therapy resulted in a rapid decline of surgical treatment of parkinsonism altogether.[21–23]

In the decades thereafter, pallidotomy for Parkinson's disease was almost completely forgotten. It was performed only exceptionally and it was not even mentioned any longer in standard textbooks of functional neurosurgery. In parallel there was also a decline of pallidotomy in other movement disorders such as dystonia with thalamotomy having been regarded the procedure of choice historically by many investigators.[24] The comprehensive textbook *Stereotaxy of the human brain* which was published along with the first edition of the canonical Schaltenbrand and Wahren stereotactic brain atlas in the early 1980s did not even list "pallidotomy" in its index.[2,25]

There were several developments that sparked the reinterest in functional neurosurgery for the treatment of movement disorders since the mid1980s. Certainly, one of the most important aspects was the rather spectacular introduction of autologous transplantation of adrenal medullary tissue to the striatum published by Madrazo and colleagues in the *New England Journal of Medicine* in 1987.[26] Of course another important measure was the introduction of "modern" deep brain stimulation which was first applied to thalamic targets and soon thereafter to pallidal targets as well.[27,28] About the same time

new models for the pathophysiology of the basal ganglia in parkinsonism and other movement disorders were developed demonstrating the crucial role of both GPi and subthalamic nucleus (STN) within the basal ganglia circuitry.[29,30] Only now it became possible to explain bradykinesia as a consequence of dopamine deficiency, and in the same line of thoughts to understand the underlying processes for its improvement after basal ganglia surgery.[31]

When Laitinen and colleagues published their manuscript in 1992 they confirmed the findings published in Svennilson's paper and they could also clearly show that pallidotomy indeed ameliorated bradykinesia and other hypokinetic symptoms. Furthermore, they demonstrated that not only parkinsonian symptoms were improved but also the side effects of chronic levodopa therapy such as fluctuations and dyskinesias. Undoubtedly, Laitinen's publication did not only spark the renaissance of pallidotomy for treatment of Parkinson's disease and dystonia, but it also laid the grounds for introducing the posteroventral lateral GPi as a target for deep brain stimulation in dystonia a few years later.[32,33] Pallidotomy became the most important treatment for Parkinson's disease in the 1990s.[3,6,13] Despite this, however, the propagation of deep brain stimulation, with its enthusiastic acceptance in the neurological community and its aggressive marketing, along with the discovery of the STN as a most effective target, made radiofrequency lesioning an established but second-line treatment,[34] and pallidotomy is only rarely performed nowadays for parkinsonism—possibly falling again into oblivion.

We assume there will be another time when pallidotomy will be rediscovered once more and the manuscripts of both Svennilson and Laitinen with their almost prophetic insights will be reevaluated again. Presently, we already see a re-emergence of lesioning surgery in the form of MR-guided focal ultrasound and other techniques.[35] Certainly, there is a need for functional neurosurgeons worldwide to preserve knowledge and skills about therapeutic lesions in movement disorders surgery. It has often been said that history would repeat itself and the disappearance and reappearance of pallidotomy would be an example for that. We do not think at all that this is the case. Rather the re-introduction and the re-evaluation of "historic" procedures such as pallidotomy is informed by new scientific insights which establish completely novel frameworks for our understanding of pathophysiology and hypothesis-driven therapy.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

J.K.K.: 1A, 1B, 1C, 3A, 3B

F.W.F.: 1C, 3B

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Joachim K. Krauss, MD Filipe Wolff Fernandes, MD

Department of Neurosurgery, Hannover Medical School, Hannover, Germany

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