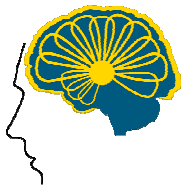
SoniModul

Incisionless Therapy of Functional Brain Disorders



Some unclassical considerations on the mechanisms and neurosurgical treatment of Parkinson's disease

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The classical message today about Parkinson's disease (PD) is that it is a „neurodegenerative" progressive disease, and that treatments, drugs and neurosurgery, can only reduce its symptoms but not stop its progression.

I would like to make here a series of points questioning some established ideas about this disease, to test if we are facing scientific facts or dogmas. For one, the « neurodegeneration » idea is questionable and represents a most severe emotional load for the patients, a sort of Damocles sword hanging over their heads and threatening the essence of what they are. Secondly, the idea that neurosurgical interventions can only be symptomatic has also to be reconsidered.

Thalamocortical rhythmic overactivity as mechanism of PD

Dopamine-producing cells in the pars compacta of the substantia nigra are known to be very fragile, so that multiple internally- or externally-generated insults may reduce their number along the years. Such insults may be : 1) externally, toxic products like pesticides, or 2) internally, cell mechanisms like inflammation, oxydative stress, calcium toxicity, excitotoxicity and stress-related glucocorticoid overproduction.

It is to be noted that dopamine has been shown through numerous animal experiments to have mainly a function in the reward, but not in the motor system. Its role as trigger for the development of PD is through the activation of a chain reaction along basal ganglia, thalamus and cortex, which will be described below.

Any treatment which would protect nigral cells would be most welcome, but because there are many different disease evolutions, from slight to severe, which cannot be foreseen, such an early treatment would have to be non-invasive.

Single cell recordings in the human thalamus as well as quantitative electroencephalographic studies have shown that, due to the reduction of dopamine in the striatum, increased neuronal activity of the internal part of the globus pallidus (GPi) causes a tonic overinhibition of the pallidal-recipient thalamic relay cells leading to a thalamocortical anomaly, named thalamocortical dysrhythmia (TCD), characterized by an overproduction of thalamic low threshold calcium spike bursts and a consecutive increase in low and high frequency EEG power. See Magnin et al. (2000) and Moazami et al. (2008). The knowledge of this chain reaction allows to distinguish 1) a source to the anomaly, i.e. the dopamine loss, 2) its generator, i.e the thalamocortical overactivity, and 3) its executors, i.e. the involved cortical areas. The available literature allows to envisage a production of tremor mainly by the dorsolateral premotor cortices, of rigidity by the supplementary motor area (SMA), and of akinesia by the anterior part of the SMA, also called preSMA.

The immense majority of the output of the basal ganglia passes through the globus pallidus, internal part and the pars reticulata of the substantia nigra, which both send inhibitory gabaergic axons to the thalamus. If one adds the fact that the main input to the basal ganglia comes to the striatum from the majority of cortical areas, one may consider the cortical-basal ganglia-thalamic pathway a feedback path from the cortex to the thalamus. By chance, there exists a second path from cortex to thalamus, i.e. the direct and massive

cortico-thalamic path, originating also from the whole cortical mantle. We shall see below how relevant these observations may be.

Thalamo-cortico-thalamic loops, together with cortico-cortical connections may be seen as the two basic network components at the source of the production of input, ouput and internal hemispheric functions (Llinas et al. 1998). The thalamocortical rhythmic and coherent dynamics has been the subject of numerous EEG and MEG studies.

The pallido-thalamic tractotomy : the subthalamotomy for PD

As the parkinsonian anomaly is passed to the thalamus mainly through the pallido-thalamic tract, and in view of the above-mentioned central relevance of the thalamocortical network for all hemispheric functions, an intervention to treat PD should be optimally placed either in the pallidum or on the pallido-thalamic tract in the subthalamus. As reviewed in Aufenberg et al. (2005), subthalamic interventions have been performed already in the sixties. We have reactualized this approach over the last 15 years based on anatomical and neurophysiological data.

We consider primarily for surgical indication the criterion of dopamine-resistance, be it the loss of efficiency (off phenomenon) of dopamine or the on-off fluctuations with dyskinesias. Dopamine-resistance indicates that the pallidal overinhibition of the thalamus is no longer controllable by the income of L-dopa into the striatum. It may be proposed that this overactive pallidothalamic path has lost its normal function, providing the possibility to interrupt it without negative consequences, but with the goal to free the thalamocortical network from deleterious pallidal overinhibition. Our choice of the H1 field of Forel in the subthalamus is based on strategic anatomical reasons presented in Gallay et al. (2008) and this surgical option has been called pallidothalamic tractotomy (PTT). In substance, this target location allows the best possible coverage of the pallidothalamic path with the smallest possible lesion volume. To be prethalamic is in our view essential, because we want to leave the whole thalamocortical network intact, which is responsible (among others) for the motor functions we want to improve.

The second important criterion for performing a PTT is the maintenance of sufficient reserves in the thalamocortical system, which can be estimated by the analysis of the amount of brain atrophy on MR images and by an assessment of cognitive functions. Particularly important is the corticothalamic projection, the largest in the brain hemispheres and the one able to maintain

an adequate thalamic input in the absence of the surgically severed dysfunctional pallidothalamic tract. See the next chapter for analysis of the relevant cell losses leading to reduced thalamocortical reserves.

The results (Aufenberg et al. 2005) can be summarized as follows: mean symptom relief covering all symptoms as listed in the Unified Parkinson Disease Rating Scale (UPDRS) was between 50 and 60%, the mean improvement of quality of life 67%. Half the patients could stop their drug intake. To be expected due to the oscillatory dynamics of the thalamocortical system, symptoms, particularly tremor, receded progressively over time during the first postoperative months, a sign that this system establishes a new resting state, closer to or at the norm. The PTT can be performed on both sides if necessary. Context-sensitive, often patient-specific, mainly anxiodepressive psychoemotional phenomena (see below) were seen. Cognitive executive and memory functions were rarely affected, either positively or negatively (variable degrees of slowing of some executive functions unrelated to the unilaterality or bilaterality of the PTT). In a study on the way now with focused ultrasound, no postoperative cognitive deficits were observed, and the Hospital Anxiety and Depression Scale remained unchanged.

The symptom improvements were stable over 5 years, an observation which allows to question a most active dogma in this field: the impossibility to stop the disease progression. We may now interpret that former studies and approaches, particularly with Deep Brain Stimulation (DBS), were not in position to liberate the thalamocortical network well enough to prevent the maintenance/progression of the parkinsonian TCD.

Cell losses beyond the substantia nigra

That abnormal cell loss happens in the parkinsonian brain is obvious. Instead of placing the problem of cell loss globally under the title « neurodegeneration », it might be most relevant to examine if different origins of these cell losses are present, and if yes what are the practical implications to be drawn out of this knowledge. The concept of degeneration has a less than optimal history. It was central, in the 19th and beginning of the 20th century, to the concept of « devolution », also called « degenerative or backward evolution », considered as causal for weakening of species and races, causing the appearance of defective, disadvantageous and retrograde primitive traits. These were correlated to the development of health and intelligence problems, including alcoholism and criminality, and lead to the proposal and application of eugenic practices in the beginning of the 20th century. In this context, I

would much prefer that our modern medical environment uses the more adequately descriptive and neutral terms of cell loss or cell death.

I have already discussed that nigral dopaminergic cells are very fragile, a fact which makes their decrease along the years unsurprising. There are however other causes of cell loss. The first ones, calcium toxicity and excitotoxicity, can be put together as two mechanisms directly related to the presence of the TCD. TCD indeed causes an increased inflow of calcium into the cell everytime a low-threshold calcium spike burst is produced. In addition, the increase of high frequency EEG power seen in TCD may correlate with excitotoxic phenomena in the cortical areas where these high frequency power increases happen. These two phenomena are in position to cause potentially widespread cortical, striatal and thalamic cell death. We have observed large variations along time of the cortical resistance to cell loss between patients, due to as yet unknown reasons. The presence of these toxicities and their suppression by the PTT bring this intervention beyond the symptomatic and causal levels into the protective domain. Another group of more general cell loss mechanisms is related to general stress and comprises glucocorticoid overproduction, inflammation and oxydative stress. That these mechanisms may be relevant here is impressively demonstrated by animal research, demonstrating that stress accelerates neuronal loss and exaggerates motor symptoms in an animal model of Parkinson's disease (Smith et al. 2008).

The psycho-emotional factor

Having a brain disorder in itself is no easy task to master for anybody. If this disorder is claimed to be a progressive unavoidable brain melting down with its associated deficits, we can imagine the immense emotional challenge at hand! The situation corresponds to the imposition of a threatening Damocles sword above the heads of the patients, and a perfect paradigm for a « pointing the bone » threat as described in ethnology, i.e. the block of brain and then body functions due to a imposed and believed death threat. I mentioned above the demonstrated relevance of stress in the parkinsonian experimental domain.

Our quantitative EEG studies have demonstrated overactivies in the expected motor areas (mainly premotor dorsolateral, cingulate motor and SMA) but also in widespread paralimbic/associative, i.e. psycho-emotional cortical areas (Moazami et al. 2008). The latter may be due either to the disease-related pallidal overinhibition of paralimbic/associative thalamic nuclei,

or to the activation of the emotional thalamocortical system by the threat of the neurodegeneration concept. Paralimbic/associative areas are in close vicinity to the mentioned motor areas, and the cingulate motor maps represent a place where the motor and psycho-emotional systems come together. This underlies the normal psychomotor continuum (no movement without a concept or emotion at its source) and explains the activation/maintenance of motor symptoms, particularly axial akinetic manifestations, by overactivities set in the psycho-emotional network. As an example, a patient we had treated with success on both sides with impressive relief of all parkinsonian manifestations, decided to travel back one year after the treatment to his distant birthplace, an activity which had been rendered impossible for years by a invalidating gait akinesia. He had been able to stop drug treatment after his bilateral PTT. He traveled by train, met there old friends and family members. During one meeting, he was asked what had happened to him. He explained that he had had Parkinson, that he had been operated and that he was doing well now. A well-intentioned friend immediately told him that he knew that nobody can be cured from this disease. The patient had to be brought back in emergency to Switzerland because of massive gait imbalance, which started just after the mentioned discussion and made an independent trip back impossible. It took more than a year of psychotherapeutic support for him to be again able to walk without aid.

These comments fit well with the demonstration in the literature of a strong placebo effect in Parkinson's disease.

The incisionless transcranial MR-guided focused ultrasound technique

TcMRgFUS allows to ablate with heating, with a submillimeter precision, any chosen target area in and around the thalamus without skin incision nor skull opening. This allows a suppression of all risks related to skull and brain penetration. Focused means that 1024 ultrasound waves, each of them innocuous for brain tissue, converge in the target, where sonic energy gets transformed in thermal energy in an area of only 3-4 mm diameter with sharp borders. The desired temperatures are between 55 and 60 degrees Celsius, and the obtained target temperature increase is checked thanks to MR-thermometry. This allows a most important, real-time control of the realized work in the target, and forbids the production of an unseen and undesired thermal increase beyond the target. This procedure provides the patient with an optimization of precision and safety.

We have now demonstrated that, as expected, the TcMRgFUS technology allows to perform a PTT with same results as with electrode penetration and radiofrequency thermocoagulation, but surely with increased (submillimeter) precision and most significantly reduced risks.

Conclusions

1) The loss of dopamine cells is in itself unexceptional, due to common and multiple causes. This loss can however trigger a potentially deleterious chain reaction leading to the clinical picture of idiopathic Parkinson's disease. Any progress in the developments of early protection techniques for dopamine cells would be most welcome, because they might reduce the incidence of the disorder both in younger and older age. As we cannot know when and how much the thalamocortical system is going to become overactive, it is not (yet) possible to be preventive at this level, but we do have the possibility to liberate it surgically from pallidal overinhibition, reinstating a more normal thalamocortical dynamics. In a better world for PD patients, the following three points would have to be implemented: 1) a better protection of nigral dopaminergic cells by the development of new protective techniques, by a reduction of toxic factors in our environment, and by the support medicine should provide to patients of their self-healing capacities, reducing thus conceptual and emotional stress, 2) the intake of L-Dopa considered by patients as a therapeutic causal and thus protective factor, and 3) the application if necessary of the described causal surgical approach against too strong a TCD.

2) Claiming that interventions can reduce symptoms but not stop the evolution of the disease should be replaced by efforts to test these interventions for their possibility to fully liberate or not the thalamocortical system. If yes, a given intervention can become symptomatic but also causal and protective for the brain. It should provide long term stable results and the possibility to stop drug treatment. If in addition it spares the thalamic and cortical partners at the source of hemispheric functions, it should be appliable on both sides. These criteria are fulfilled by the PTT.

3) The ghost of « neurodegeneration » should at best be abandoned, as it represents a massive disease concept inductor, feeding on the threat

and fear of brain annihilation. Instead, well qualifiable cell death mechanisms should be considered as to their cause and effects, e.g. the calcium and excito-toxicity due to the TCD, which is potentially able to deprive the thalamocortical network of cells. Thus, a cell death cause appears which may be controlled by a surgical treatment.

4) The integration of the psycho-emotional dimension is important in all our field as it is in the whole of medicine! In the case of Parkinson's disease, it is fundamental, because of the Damocles sword of brain threat placed over the heads of our patients. A patient of mine told me one day that the oncologist of his friend was kinder to him than his neurologist to himself, because he gave him at least a chance! Parkinsonian patients deserve to be liberated from unbased and vague concepts and dogmas, and offered what modern high-tech and also integrative medicine can give them.

5) As for Parkinson-Plus syndromes, characterized by extensive and widespread cell losses in the whole brain, there is no explanation yet as to their cause. In view of the fact that stress in animal models can kill cells, it might be relevant to have a deeper look into this potential causality.

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