To Dystonia Europe

Next research targets: Combination of neurovascular decompression and brain research in cervical dystonia / Neurovascular conflicts in laryngeal dystonia / Peripheral nervous effects of deep brain stimulation

Dear Mrs. Benson, dear Mrs. Avery,

In January 2017 we have informed you about our attempt to initiate research into peripheral nervous factors in the causation of dystonia. You wished us success in our work and wrote that you "look forward seeing how our research develops in due to course". In this letter, we inform you about the result and our next steps. Maybe you would like to support our effort to find suitable researchers.

Probably you remember that we concentrate on the hypothesis that dystonic symptoms are caused by faulty sensory feedback. The sensory organs in the muscles are called muscle spindles. Distortion of sensory information could be caused by inappropriate activation of muscle spindles by the brain, by inappropriate transmission of signals in the nerves, or by abnormities within the muscle spindles themselves. Whereas most dystonia researchers accept the dominance of brain research, we clearly emphasize the importance of research into the causal role of peripheral nervous abnormities.

In 2017 we formulated a research proposal concretizing our model of causation for cervical dystonia and suggesting to record sensory signals from neck muscle spindles via microneurography. We sent this proposal directly to experts in the field of muscle spindle physiology. Michael Dimitrious (University of Umea, Sweden) wrote us that he is "glad work is planned to look into links between dystonia and proprioception" and that he believes that the "role of faulty proprioception in dystonic and other neuromuscular ailments has been vastly underestimated". However, he believes that the current technology is not suited for recording the sensory output from neck and shoulder muscles. Gerald Loeb (University of Southern California) has a similar opinion, writing that "microneurography of spindle afferent activity would be useful but unlikely to be feasible in neck muscles, especially in dystonic patients".

Therefore, we will promote direct research into the role of structural abnormities of the peripheral nervous system that could cause faulty sensory feedback to the brain. Concretely, we will promote research into the role of neurovascular conflicts in dystonia. Neurovascular conflicts are abnormal contacts between blood vessels and nerves that impair nerve function. The surgical repair of such abnormities is called neurovascular (or microvascular) decompression.

You surely know that neurovascular decompression has been acknowledged as causal therapy of hemifacial spasm, but it is less well known that neurovascular conflicts have also been diagnosed and surgically repaired (for more than 20 years) in patients suffering from "spasmodic torticollis" (PubMed

list). The authors of these studies probably avoided the term "cervical dystonia" because it is commonly associated with theories favoring an important causal role of abnormal basal ganglia activity. Whereas the results of neurovascular decompression have been excellent in 80% of patients with hemifacial spasm, fewer cervical dystonia patients have achieved this level of improvement, as you can see, for example, in two studies of the University of Shanghai (2014, 2017). However, this is the only dystonia therapy that repairs real structural defects that are diagnosed individually, so this diagnosis might be an interesting first step to patients with cervical dystonia who would basically accept therapies including surgery but do not like the idea of having electrodes implanted in their brains. As Dystonia Europe represents also patients with hemifacial spasm, you could present neurovascular decompression on your website as a therapy for these patients and it would be fair to mention that neurovascular conflicts can exist in patients with cervical dystonia, too (this is a Canadian example).

We will proceed as follows.

1. **Combination of neurovascular decompression and brain research**. As promised in our research principles, we will always attempt to reduce the number of primary causative factors in dystonia theories. Effective peripheral therapies are useful tools for ranking brain abnormities in the causation hierarchy. White matter abnormities in the brains of patients with cervical dystonia, for example, were absent four weeks after botulinum toxin injection, which demonstrated that these structural brain abnormities were not higher in the causation hierarchy than the peripheral symptoms and their sensory feedback to the brain. We believe that neurovascular decompression is even better suited to classify the causative role of brain abnormities than botulinum toxin, because the symptoms do not recur periodically, so it is possible to observe the long-term effects on the brain. Therefore, we will propose studies on three questions: 1. What is the percentage of patients with cervical dystonia who have neurovascular conflicts? 2. Do cervical dystonia patients with neurovascular conflicts also have the structural and functional brain abnormities associated with cervical dystonia? 3. Which abnormities disappear after successful neurovascular decompression? We will show a particular interest in basal ganglia activity, because this is the brain abnormity that is believed to play an important role in the cause of dystonia We will also look at whether the basal ganglia activities before and after successful botulinum toxin injections have already been compared, as we have not found any publication in this regard.

2. **Research into neurovascular conflicts in other types of dystonia**. First of all, we will propose to search for neurovascular conflicts also in laryngeal dystonia. We chose this type of dystonia for three reasons. First, the basic aim of our project is to combine stuttering and dystonia research and we hypothesized a laryngeal link. Second, neurovascular conflicts are supposed to damage the insulating layer around nerve fibers (called myelin) and demyelinization of the laryngeal recurrent nerve has already been found in patients with laryngeal dystonia. Third, the left and right laryngeal recurrent nerves loop around and cross a sufficient number of blood vessels to be susceptible to neurovascular conflicts. In addition, the recurrent laryngeal nerve is near or even penetrating through a laryngeal ligament, which might also lead to abnormal contacts. Unlike other researchers, we do not believe that neurovascular conflicts need to be close to the central nervous system and directly cause dramatic signals to the CNS. We think that it would be bad enough if such conflicts alter the signals by which the brain activates the muscle spindles or alter the signals that the muscle spindles send to the brain.

3. **Research into peripheral nervous effects of deep brain stimulation.** The very limited symptoms of isolated cervical dystonia do not make it necessary to assume a primary

causal role of abnormal basal ganglia activity. In our model of 2017 (link on page 1) we demonstrated that distorted sensory feedback could cause all diagnostically relevant symptoms of cervical dystonia by completely normal brain functions, so that in principle all brain abnormities could be interpreted as secondary reactions that affect symptom severity without being causal. Abnormal basal ganglia activity could simply enhance the activation of muscle spindles (fusimotor activation) and thereby aggravate (pre-existing) distortion of proprioception. Deep brain stimulation (DBS) might exhaust basal ganglia activity and thereby reverse this unfavourable mechanism. Since the sensory signals from dystonic muscles are unlikely to be correctly recordable, we will deal with three questions. 1. What side effects can DBS produce in non-dystonic body parts? 2. Could these side effects indicate that DBS reduces the fusimotor activation of muscle spindles? 3. Is it possible to record signals from muscle spindles in these non-dystonic parts of the body (using microneurography) to compare values with and without DBS? We suppose that, for example, muscles involved in handwriting would be a suitable target.

In these steps, already known techniques would be used in new combinations. European researchers, however, have contributed little to the recent publications on neurovascular decompression in cervical dystonia, and we fear that an ideological separation might complicate the combination with brain research. Therefore, we also consider contacting Chinese researchers.

We read on the Dystonia Europe website that you "provide an international platform on the European level that will stimulate research for more effective treatment and, ultimately, to find a cure". Our research proposals are directly relevant to dystonia therapy, but your website suggests that you represent only patients who interpret dystonia as a brain disease (What about this Italian patient ?). If you find our research proposals interesting and would like to support our efforts to find and motivate suitable researchers, please respond by **April 14, 2018**.

Kind regards,

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