Poznań, 21 May 2023

Study protocol

"Comprehensive assessment of patients with dystonia treated with botulinum toxin"

version 1 – 21 May 2023

Focal dystonia is a group of movement disorders characterised by repetitive, twisting muscle contractions causing abnormal posture. It is estimated that dystonia as an isolated condition occurs in European countries at an average rate of 16.4/100,000 people. Many studies have found that the disease contributes to impaired professional functioning, is associated with the onset of anxiety disorders and social isolation, and thus significantly reduces patients' quality of life. The problem is certainly underestimated, as due to its rare occurrence, many patients remain without an accurate diagnosis for several years after the first symptoms appear.

Although the disease has been described since ancient times, its exact aetiopathogenesis remains unclear. The increased activity of muscle groups is caused by signalling disorders within the neural loops in the central nervous system. Certain genetic mutations responsible for the onset of dystonia, especially generalised dystonia and dystonia manifesting in childhood, are known, but in the case of focal dystonia, it is usually not possible to find a pathogenetic basis. Therefore, causal treatment is not available (except for levodopa-responsive dystonia, which will not be the subject of this study). The commonly accepted symptomatic treatment methods include repeated intramuscular administration of botulinum toxin A, rehabilitation and pain management, as well as the use of the neurosurgical method DBS (deep brain stimulation), which will also be excluded from the analysis in this study due to its limited availability.

The aim of the project is a comprehensive assessment of patients with dystonia treated with botulinum toxin, including neurological examination, functional and neurophysiological tests, radiological findings, serum biochemical concentrations and neuropsychological tests.

Specific objectives:

1. Verification of the effect of botulinum toxin A injection on posture, motor function and gait in patients with cervical dystonia.

2. To assess the effect of botulinum toxin A injections on the severity of anxiety disorders and symptoms of social isolation in patients with focal dystonia.

3. To assess cognitive function in a group of patients with focal dystonia and correlate it with biochemical indicators of blood-brain barrier integrity.

4. Determination of therapeutic goals (pharmacotherapy, physiotherapy, psychotherapy) in patients with focal dystonia. Accurate determination of therapies supporting symptomatic treatment with botulinum toxin A may increase the effectiveness of treatment and reduce the total costs of treatment and the social stigma that the disease imposes on patients.

5. Raising awareness of the disease in the medical community and popularising the results of

the study among general neurologists, physiotherapists and psychologists through publications in professional journals.

Material

The study is planned to be conducted between 1 July 2023 and 31 December 2024 on a group of approximately 100 people, aged 18 to 60, diagnosed with focal dystonia.

Patients will be recruited by neurologists from the J. Struś Multispecialist Municipal Hospital in Poznań at ul. Szwajcarska 3. The first group will consist of patients treated in the National Health Fund Programme for the Treatment of Focal Dystonia with Botulinum Toxin for a minimum of 3 months. The second group will consist of individuals newly qualified for treatment in the Botulinum Toxin Treatment Programme who have not previously been treated with botulinum toxin injections.

The inclusion criteria will include:

- age 18-60 years,
- diagnosis of focal dystonia,
- patients qualified for treatment in the National Health Fund Programme for the treatment of focal dystonia with botulinum toxin (standard qualification under the conditions specified in the National Health Fund Programme, performed by a specialist neurologist with experience in botulinum toxin treatment)
- ability to establish logical verbal communication in order to obtain voluntary and informed consent to participate in the study,

The following will be excluded from the study:

- pregnant women;
- persons with confirmed allergy/hypersensitivity to the neurotoxin complex or any of the components of botulinum toxin A;
- patients with hemifacial spasm (Meige's syndrome);
- patients after DBS implantation;
- patients with comorbidities that prevent the tests planned in the study protocol from being performed:
    - NYHA heart failure above II/III
    - mobility disorders (patients with paresis, unable to walk independently)
    - chronic kidney disease (GFR<60 ml/min/1.73 m^2)
    - clinically significant visual impairment confirmed by ophthalmological examination
    - impaired logical verbal communication (aphasia, mental retardation, moderate to severe dementia, mental illnesses preventing neuropsychological testing, e.g. severe depression, paranoid schizophrenia - confirmed by psychiatric examination)
    - autoimmune diseases
    - coagulation disorders, severe anaemia or leukopenia

- persons who do not consent to the study.

The study plans to conduct:

1. A questionnaire survey to determine age, gender, education, type of work, time of onset of

the first symptoms of dystonia, date of diagnosis, comorbidities, and medications used for chronic and acute treatment.

2. Neuropsychological tests to assess cognitive function (MoCA, MMSE, ACE-I EpiTrack) and assessment of the severity of anxiety disorders (Liebowitz Social Anxiety Scale), depression (Beck Depression Scale), pain (NRS scale), (Beck Depression Scale), pain (NRS scale), sleep disorders (Epworth Sleep Scale).

3. Functional assessment – mobility and posture examination: posturography, Up-And-Go Test, Tinetti test, before and 4-6 weeks after botulinum toxin A injection.

4. Assessment of autonomic nervous system function in patients before and after TB treatment (Schelong test – blood pressure measurement in a lying position and after standing up).

5. Collection of 2 x 5 ml of venous blood from the radial vein – 1st tube 5 ml before and 1st tube 5 ml 4-6 weeks after botulinum toxin A injections, in order to test the concentration of, among others, the S100B molecule (S100 calcium-binding protein B), NSE (neuron-specific enolase), OCLN (occludin), CLN5 (claudin-5), zo-1 (zonula occludens-1), sPECAM-1, sICAM-1, myoglobin, creatine kinase CK, light neurofilaments, creatinine and eGFR, urea, sodium, potassium, iron, ferritin, blood count.

6. Analysis of radiological examinations routinely performed as part of the mandatory qualification for treatment (MR or CT of the head or neck).

7. Muscle examination using ultrasound elastography – during a non-invasive ultrasound examination before and 4-6 weeks after botulinum toxin A injections.

8. Neurophysiological examination: assessment of muscles in EMG, assessment of CSP (Cutaneous Silence Period) from muscles involved in the dystonia pattern according to the Col-Cap concept.

   The examinations will be performed on the day of the planned botulinum toxin A injection – before treatment (first assessment) and 4-6 weeks after botulinum toxin A injections (second assessment).

   The above activities will not delay the treatment with botulinum toxin A injections.

   The collected results will be subjected to statistical analysis.

   The results obtained in the study will enable the identification of the most important medical problems in the analysed group and will allow for the targeting of further research on the aetiology and treatment methods of dystonia.