

Info-research...

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It has been demonstrated that there is a deficiency in serotonin and in thiamine in patients with ataxia as well as phenomena of cellular destruction on the level of the cerebellum. Previous works of Dr. Botez and our neurology of behaviour laboratory demonstrated the improvement in the symptoms of ataxia with the use of, in a simple treatment, amantadine (Symmetrel) as a neuroprotector agent and of Tryptophan as a replacement substance. Following this, an approach associating at the same time a substitution treatment with Tryptophan and thiamine and a neuroprotection therapy with amantadine (Symmetrel) allowed an improvement in the symptoms of ataxia, and we believe a certain stabilization of the disease.

Under pressure from Dr. Botez, a clinic specialized in hereditary-degenerative ataxias was created on the Hôtel-Dieu of CHUM campus of which the first goal is to assure the quality of care to the patients with ataxia by seeing to detecting systemic cardiac complications as well as other needs so that these patients with ataxia can profit from research efforts and have access to a treatment experiment more rapidly.

In a manner more specific to the level of the research work, these were divided into a clinical section and a fundamental section. The clinical section was first initiated with amantadine (Symmetrel) then Tryptophan and is presently continuing with a triple therapy associating at once thiamine and Tryptophan as a substitution therapy and amantadine as a neuroprotection therapy as previously mentioned.

Following these works, a certain improvement in the symptoms of ataxia, dysarthria and respiratory troubles encountered in patients with ataxia manifested by periods of apnea, i.e. a stop of breathing during sleep, was therefore demonstrated. In collaboration with Dr. Pierre Mayer, lung specialist and director of the Sleep Laboratory of CHUM, we studied the respiratory troubles during sleep in ataxic patients without treatment and with the treatment mentioned above. We were able to demonstrate a marked improvement at once in the periods of apnea of the central type and of the peripheral type as well as in dysarthria or spastic dysphonia. This clinical research also includes a clinical neuropsychological evaluation section which is done in collaboration with Madame Thérèse Botez-Marquard, neuropsychologist.

As for the fundamental section, it necessitates at once neurobehavioural and motor studies as well as neurochemical correlations in an animal model of ataxia in a mouse. One may wonder why an animal model in order to evaluate therapeutic approaches in a human. The relevance of the animal model is that it is easily accessible and that during a relatively short period we can see the impact of different substances. Furthermore, in a mouse one finds mutant clones with ataxia and therefore it offers an interesting model at once for Friedreich's ataxia with the mouse called dystonic, and for olivopontocerebellar degeneration with the mouse called Lurcher. In fact, we can find in both models anatomical and neurochemical abnormalities similar to the human disease.

We have developed with these mice models evaluation methods of behaviour and of motivity in the perspective of validating the beneficent effects already described in the human with amantadine (Symmetrel) and Tryptophan and thanks to the collaboration of the Laboratory of Dr. Reader, researcher in neurochemistry in the department of neurological sciences of the University of Montreal, of establishing correlations between behavioural and motor changes and the neurochemical changes on the level of the brain of mice and the response to different treatments.

In our Laboratory, Dr. Robert Lalonde, of whom the expertise in animal behaviour neuropsychology is recognized internationally, perfected different evaluation methods of these tests and thanks to the work of Mrs. Nathalie Le Marec, Ph. D. in behavioural neuropsychology, we will be able to continue to work on these animal models and use them in order to validate or not the pertinence of using different therapies as much of substitution as of neuroprotection.

Until the present, we completed studies in relation with an agonist of serotonin, Buspirone (Buspar). We have decided to study this substance following contradictory results on the clinical level reported in the literature. We are now colligating these results.

Following the publication of the results demonstrating an abnormality on the level of the metabolism of iron on the mitochondrial level, it was suggested to simply use a substance called "Deferoxanine" (Desferal) which has the effect of capturing the iron in the organism and of eliminating it (chelating effect). Therefore, we have studied in the animal model of a mouse the effect of Desferal on survival and on behavioural and motor skills. This study is now over and the results are at the stage of analysis.

We are presently in the course of studying a substance called Remacemide of which the chief role is that of being an anticonvulsant (antiepileptic) but which has the characteristic of linking itself in a preferential manner to the NMDA receptors on the level of the cerebellum and blocking them from acting thusly as a neuroprotector. In fact, stimulation of these NMDA receptors has the effect of creating an abnormal stimulation of the cerebellar cells furthering an abnormal entry of calcium which can

bring about cellular death. By blocking these NMDA receptors, we believe that we can protect the cells of the cerebellum limiting thusly the destruction of the cerebellum and of its connections. We have already demonstrated in our laboratory on the level of the model of a mouse an improvement in behaviour and motor skills thanks to amantadine (Symmetrel) which has an effect on the level of dopamine and which acts as a neuroprotector by blocking the NMDA receptors. This study with Remacemide is therefore being pursued and should end during the month of March. As already mentioned above, all these neurobehavioural and neuropharmacological studies are being done in correlation with the evaluations of the neurochemical studies on the level of the brain of mice.

On the level of future research, from a clinical point of view we foresee attempting to apply the results obtained on the level of the animal model if we can demonstrate that there were benefits in relation to the agents already evaluated just as we intend to revise the clinical neurobehavioural studies in order to verify if we can detect a stabilization of the disease or not. Besides, from the fundamental point of view and the help of the animal model already mentioned and the interaction with Dr. Reader's laboratory in neurochemistry, we continue to evaluate different substances acting either as a neuroprotector or as a replacement agent.

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