CONFERENCE REPORT

The Torsion Dystonias

The Fifth Dystonia Medical Research Foundation Workshop was held on February 9 and 10, 1984, at The University of Calgary Medical School with the support of the Alberta Heritage Foundation for Medical Research.

A total of 13 papers were presented. Nine of these represented progress reports on ongoing research on dystonia; the other four were "state of the art" lectures dealing with the following subjects: "Torsion dystonia in Sweden" (Dr. Gosta Holmgren), "Neurobiology of Sleep" (Dr. Jon F. Sassin), "Positron Emission Tomography in Movement Disorders" (Dr. Wayne Martin), and "A Polymorphic DNA Marker Genetically Linked to Huntington's Disease" (Dr. James Gusella).

The first progress report was presented by **Dr. David Marsden** (London, England) who discussed the pharmacologic mechanism of torsion dystonia and also reported on the status of the European tissue center.

Dr. Marsden is in charge of a Dystonia Referral Center which treats about 500 patients with primary and secondary dystonia. The term "secondary" dystonia is used for those forms of torsion dystonia (TD) caused by an injury to the brain, usually vascular in nature. CT scans of patients with secondary TD indicate that the putamen is the part of the basal ganglia which is usually affected. In Marsden's experience, good results in relieving the symptoms of dystonia can be obtained with large doses of anticholinergics. Although there has been some concern that such large doses may adversely affect intelligence, Marsden reported that psychometric testing has shown this not to be the case. Some other drugs that have been effective in some patients include carbamazepine, L-dopa, bromocriptine and lisuride. Familial myoclonic dystonia may respond to clonazepam and to alcohol.

In axial dystonia, Marsden has been using a "cocktail". This consists of tetrabenazine (25 mg tid.), and progressively increasing dosages of Pimozide, a dopamine receptor blocker, structurally related to haloperidol (Haldol). This drug is started at 2 mg, and the dosage is increased until signs of Parkinsonism develop. These are controlled by Artane in doses ranging from 6-30 mg a day. In the treatment of torticollis, Marsden has found amantidine best. Haloperidol, in his experience, oversedates patients.

The Tissue Collection Center has obtained three brains of patients with TD. These will be submitted for anatomical and biochemical studies.

In the ensuing discussion, Dr. André Barbeau (Montreal) commented that 5 of his 14 TD patients have responded well to L-dopa, and have maintained their improvement over several years. He prefers to use levodopa in small dosages (less than 2 gm/day) without the addition of carbidopa. He noted similarities between these cases and the Segawa variant, a form of TD found in Japan, which has marked diurnal variations and responds well to L-dopa. Marsden and Dr. Howard Hurtig (Philadelphia) noted that in addition to the Segawa variant, juvenile Parkinsonism and exercise-induced TD also respond well to L-dopa. In the experience of Dr. John H. Menkes (Los Angeles), Ashkenazi Jews with TD almost never respond to L-dopa. Dr. Stanley Fahn (New York) commented that he has had some success in treating blepharospasm with baclofen (Lioresal).

Dr. Stanley Fahn (New York) summarized the activities of the Dystonia Clinical Research Center in New York.

This research center follows more than 500 TD patients, and is currently engaged in a variety of research projects, some of which are in collaboration with other groups. One of the activities of the Center is to serve as a tissue resource and tissue culture center which maintains specimens of blood, CSF, and skin fibroblasts from TD patients for the use of scientists at the Center and at other institutions throughout the world. The CSF concentrations of a variety of substances have been studied. These include GABA, amino acids, somatostatin, arginine vasopressin, TRH, ACTH, CCK, biopterin, trace elements, and monoamines. All of these have been negative up to now, with the exception of one family which had low CSF biopterin levels. The Center has also carried out a number of studies on cell membranes obtained from red blood cells and skin fibroblasts from dystonia patients, but so far, no significant abnormalities have been uncovered.

Another activity of the Center is the organization and maintenance of a Dystonia Data Base, in which extensive information about a large number of TD patients will be recorded and made accessible to all scientists interested in TD research.

Another research area of the Center is the genetics of TD. This work is a collaborative effort with Drs. Xandra Breakefield, and James Gusella. Finally, the Center has been involved in the characterization and study of animal models for TD. There are some conditions in mice and rats, caused either by spontaneous mutations or by chemically induced changes in their nervous systems, that sufficiently resemble dystonia to make them attractive models for study.

Dr. Donald Calne (Vancouver) presented a progress report on the Movement Disorder Center at the University of British Columbia.

Unlike the New York Center which studies only TD, the Vancouver center studies other movement disorders as well, employing CT scans, nuclear magnetic resonance imaging (NMR), and positron emission tomography (PET). Calne reported three cases, probably all secondary TD, in which CT and NMR studies revealed lesions in the putamen. These findings are consistent with those reported by Marsden, and suggest that particular emphasis be placed on studies of the putamen. Calne also described a family with dominantly inherited dystonia who demonstrated intracranial calcifications.

Ascertainment of patients with dystonia in British Columbia (Population 2.5 million) has yielded the following: Generalized dystonia — 17 cases, Multifocal dystonia — 21, Torticollis — 46, Writer's cramp — 15, Blepharospasm — 10.

In Alberta, 9 patients with generalized dystonia have now been identified.

Another research area of the Center deals with the treatment of the focal dystonias (blepharospasm, torticollis, oromandibular

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dystonia and writer's cramp). In Calne's experience, lisuride, at a mean dosage of 2.6 mg/day, usually offered some improvement in patients with blepharospasm; patients with torticollis respond less often, whereas patients with writer's cramp show no improvement. Oromandibular dystonia was helped by baclofen. Initial studies on cerebral glucose metabolism using PET scans were reported. Glucose is the primary substrate required by the mature brain for energy production. Dopamine has an inhibitory effect on neuronal activity, so that decreased levels of cerebral dopamine lead to increased glucose metabolism. This inverse relationship between glucose metabolism and dopaminergic activity, seen in Parkinsonism, has also been observed in focal dystonia and chorea.

Dr. Edward Bird (Belmont, Mass.) discussed the activities of the Brain Bank which was established under his direction as a repository for brains from patients with TD and other degenerative neurological disorders.

At the present time the bank contains two brains from dystonia patients. It is still a matter of controversy as to which method of preserving brain is best. Fixing in formalin is optimal for light- and electron-microscopy, whereas freezing is preferable for neurochemical studies. The best solution may be to cut the brain in half, vertically, freeze one half, and fix the other in formalin. Such an approach would obviously not be feasible in cases with hemidystonia.

The next progress report was presented by **Dr. Leon Thal** (Bronx, N.Y.) who described measurements of certain neurotransmitters and their metabolites on CSF and ventricular fluid from dystonic patients.

Dr. Thal has taken advantage of the availability of ventricular fluid from patients undergoing thalamotomy for treatment of TD and other neurological disorders. The dystonia patients were divided into childhood- and adult-onset groups. In addition, there were patients with secondary dystonia. The following neurotransmitters were measured: dopamine, norepinephrine, DOPAC, HVA, 5-HIAA, VIP, somatostatin and MHPG. Thal found that MHPG, the primary brain metabolite of norepinephrine, was decreased in both the dominant and the apparently recessive forms of childhood-onset dystonia, but not in the adult-onset group. Norepinephrine levels were decreased in the former, and, as expected, not in the latter group of patients. There were no abnormalities in the levels of VIP. The only other significant change in neurotransmitters was a 38% decrease in the level of somatostatin in the childhood-onset group.

Dr. William Jankel reported results of his work on experimental analysis of sleep in torsion dystonia.

Dr. Jankel has explored the sleep patterns of 10 patients with mild dystonia, and 12 with severe dystonia, and has compared these with controls matched for age and sex. Patients with severe dystonia took longer to fall asleep, slept less total time, and spent more time in stage 2 sleep. Patients with mild dystonia fell in between severe dystonias and controls with respect to all three measurements. Severely affected patients also displayed unusually large spindles during stage 2 sleep. Sleep spindles are EEG patterns of waves characterized by progressively increasing and then gradually decreasing amplitude. Jankel speculated on the possibility that there was a defect in the norepinephrine-locus ceruleus system, leading to overactivity of the serotonergic raphe system believed to govern non-REM sleep.

Progress in locating the gene responsible for TD was reviewed by **Dr. Xandra Breakefield** (New Haven, Conn.).

A search for the dystonia gene is currently in progress in association with Dr. James Gusella, MIT, and Dr. Stanley Fahn and their associates. The technique being used is the one that was successful in locating the gene for Huntington's Disease. A crucial element in the success of this technique is the availability of large families in which the disease can be traced from one generation to the next. This makes the autosomal dominant form of dystonia easier to investigate than the apparently recessive form. One such large family has been located in which affected members can be found in each of five generations. Blood and fibroblast samples are collected from both affected and unaffected family members. Dr. Breakefield estimated that with the probes and markers presently available to her, it is still only possible to cover about one half of the human genome. One important requirement is the availability of other large families with dystonia, and every effort should be made to locate such families and secure their cooperation in this project.

Dr. Alan Tobin (Los Angeles) has also been carrying out research aimed at identifying candidate genes for dystonia.

Recombinant DNA technology is providing increasingly powerful tools for the isolation of specific genes. Dr. Tobin reviewed some of these new tools and indicated the role they may play in TD research. Post-mortem studies of brains derived from dystonia patients should be especially valuable in providing hints as to which genes are suspect, based on any abnormalities in neurotransmitters, enzymes, receptors or other proteins.

The final progress report was given by **Dr. Frank Vincenzi** (Seattle) who discussed calmodulin activation of the calcium pump in dystonia.

Several diseases may be brought on by an abnormality in calcium ion transport across cell membranes. Calmodulin is a protein that may be a major regulator of cellular calcium concentrations by its ability to activate calcium pumps in cell membranes. Vincenzi has investigated calmodulin activated (Ca/Mg) ATPase activity in TD patients and their families. No difference in activity was found between TD patients and controls. However, when trifluoperazine was used as a calcium pump inhibitor, a significant difference was found initially in ATPase activity between the Jewish TD patients and their controls. There was no difference between non-Jewish patients and controls. These studies could not be confirmed, and Vincenzi believes that some of the discrepancies are the consequence of changes in the lipid environment of red cells, and the fact that activation of the calcium pump is dependent on the lipid environment of the calmodulin molecules in the membrane.

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