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Anticholinesterase Drugs and Epileptic Seizures

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Despite the views of many authors that migraine and epilepsy are unrelated phenomena, there is much evidence to the contrary. Davidenkov (1934) studied fifty parents with epilepsy, twenty-six of whose children had migraine. Barolin (1966) and Janzen (1969) also present evidence of a high incidence of migraine in epileptics. Owing to the success in treating migraine with anticholinesterases syntostigmin and nivalin (Ikonomoff, 1961, 1967, 1968), and the possible relationship between migraine and epilepsy, the same anticholinesterase drugs were administered to epileptics. Tentative and careful studies with syntostigmin and nivalin seemed to show that these anticholinesterases could be given with safety and apparent success. A study was therefore. undertaken of the effects of syntostigmin.

Methods

Bearing in mind the investigation by Bradley and Elkes (1957) we have started treating hereditary epilepsy with anticholinesterase drugs. An adequate choice has been made in terms of the patients, however, i.e. we have submitted to treatment only patients with a clinical picture typical of the disease, without any pathological deviations whatsoever either in the neurologic status or EEG. Moreover, we have subjected to treatment solely patients with frequent fits, e.g. a fit in the course of a few days, or at least one per month.

Fourteen patients with undeniable epileptic episodes, occurring at a minimum once a month, were studied. Nine were male and five female, the youngest was 2 years old, the eldest 65. Seven patients had grand mal and seven petit mal. In three cases, two with petit mal and one with grand mal, migraine also occurred.

The initial studies were with nivalin. The later and definitive studies were with syntostigmin, tablets of 15 mg.—a synthetic anticholinesterase preparation produced in Czechoslovakia. It has the advantage that it can be used in tablets as well as in ampoules. The treatment began with 7·5 mg. (daily), then the dose was gradually increased to 15 mg. given three times a day, within a week. This is continued until 1500 mgs. have been given. After this course of treatment, however, a 15 days interruption of the drug is obligatory, with the aim of avoiding a sharp increase of the stimulation of the parasympathetic nervous system of which early manifestations might be muscarine-like or nicotine-like signs. For a complete treatment, this course of 1500 mg. of syntostigmin, has to be given—according to the severity of the disease and the frequency of the occurrence of the seizures—4 to 6 times (between 6,000–9,000 mg.).

Results

The results of the implemented treatment followed up for three years proved to be as follows. Three patients out of 7 patients with petit mal showed no seizures; three other patients had seizures occurring more rarely; one patient showed no change. In terms of the 7 patients with grand mal the results are as follows: disappearance of seizures in one patient; spacing of the seizures and decrease of their intensity in three patients; two patients showed no clinical change; the seizures became more frequent in one patient. The small number of the patients treated allows for no more thorough discussion.

Discussion

Brenner, Merritt, Penfield, Jasper, Kreindler, Tower, Zakusov, and others assume that acetylcholine could cause the appearance of epileptic paroxysms. Recently, Bradley and Elkes have demonstrated that physostigmine causes characteristic electrical effects without behavioural change, emphasis being laid on dose level. According to these authors small doses of physostigmine bring about a change in the electrical activity without any behavioural change. The greater doses tend to provoke behavioural alerting, but this is not always accompanied by peripheral signs.

The reason that leads many authors to assume, that acetylcholine and anticholinesterase drugs provoke epileptic seizures is, in our opinion, the fact of the high dosage employed; and probably also that they have been used in cases of cortical epilepsy.

We assume that in epilepsy there exists a pathological heredity in the disturbance of balance of the biogenetic amines at a subcellular level in the vesicles containing acetylcholine, serotonin and catecholamine in the cells of the hypothalamic region.

Our opinion is that the syntostigmin resembles the epileptic paroxysms only in subcortical epilepsy, which for us has a predominantly hereditary character; anticholinesterase drugs provoke seizures in most of the cases with cortical epilepsy which in our opinion, are almost always symptomatic. We assume that this opinion of ours does not contradict the opinion by Y. Mazars, G. Mazars and Cl. Piot (1966) according to which the anticonvulsive effect of prostigmin would be very small or none in cases with cortical epilepsy, but would be marked in cases with centrencephalon epilepsy; nor does it contrast with the opinion of Celesia and Jasper (1966), who later produced local epileptiform discharges from the cortex of animals following administration of prostigmin.

The differences in the therapeutic properties of the anticholinesterase drugs used by Y. Mazars, G. Mazars and Piot, and by us in the treatment of epilepsy, are due to different effects of the drugs used—prostigmin on their side, syntostigmin on ours. The therapeutic effect of prostigmin is swift, but has a short duration; on the other hand syntostigmin functions slowly, but leads to a stable therapeutic result.

In distinction to prostigmin, syntostigmin has a good tolerance, does not have a toxic effect, and therefore can be used in pregnancy, without the risk of provoking an abortion. In distinction to prostigmin, which has to be given uninterruptedly and as a rule has only prophylactic value, syntostigmin appears to be one of the best therapeutic agents in our own clinical practice. In fact, in our experience, six to nine months treatment with syntostigmin can lead to positive results.

In conclusion, from the therapeutic point of view, the future task is to find a reliable method of diagnosis requiring an aetiopathogenetic differentiation between the subcortical and the cortical forms of epilepsy.

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