12 Gercke OL. Suicide by ingestion of amphetamine sulphate. JAMA 1945;128:1098-9.

**Letters**

**Indomethacin and propranolol combined treatment for Shy-Drager syndrome**

Sir: Indomethacin has been recently proposed for symptomatic relief of postural hypotension in Shy-Drager syndrome as well as in idiopathic orthostatic hypotension. We report the results of combined treatment with indomethacin and a β-adrenergic blocking agent (propranolol) in a patient who showed clinical signs of multiple system atrophy, autonomic failure, including orthostatic fall of the blood pressure and severe systo-diastolic hypertension when reclining. A 45-year-old woman was referred to our department because of a two year history of progressive gait disorder, speech and hand-writing difficulty, urinary and rectal incontinence, syncopal episodes lasting a few seconds, without loss of consciousness, all related to rising. No neurological illness was detected in the family. She had severe systo-diastolic hypertension for five years, untreated previously. On admission to the ward, her blood pressure reading was 210/135 mm Hg when lying, but unrecordable when standing. Neurological examination showed features of Parkinsonism (hypokinesia, amnic face, cogwheel rigidity of limbs), pyramidal signs (left sided sustained clonus, bilateral extensor plantar and Hoffmann responses) and cerebellar symptoms (gross dysmetria on finger to finger and heel to shin, poor alternating movements, dystarhic speech and tremor, both at rest and with movement). Gait could not be examined as the patient was unable to stand without fainting. Bilateral iris atrophy, positive Schirmer tests, and an atonic bladder were found. Verbal and performance IQ test indicated intellectual deterioration.

During her two months of hospital stay, blood pressure and pulse-rate were recorded three times a day. No drugs were given for the first three weeks and the patient took a free diet. The following laboratory findings including CBC, VDRL, urine analysis, CSF, liver and thyroid function tests, serum and urine electrolytes, plasma-volume, 24-hour urinary excretion of catecholamines and vanil-mandelic acid, and folicacic, urinary excretion of B12, were normal. Plasma renin activity, plasma and urinary aldosterone levels were within the normal range. ECG was unremarkable. A systemic, cardiac and renal diseases were excluded. Radiographs of skull and chest were normal. CT scan showed cerebral atrophy, but no focal softening. On EEG, there were diffuse slow waves. Autonomic failure was documented by the orthostatic fall of the blood pressure from 220/135 mm Hg to 40 systolic, recorded twice after 3 to 4 minutes in upright position, and by the ECG monitoring of heart rate variation in response to standing and during deep breathing. The R-R interval ratio at 30 and at 15 beats was exactly 1:00 and the expiration inspiration ratio was found to be less than 9%. The two latter findings were strongly suggestive of autonomic dysfunction, which was confirmed by the lack of systolic overshoot in Valsalva’s manoeuvre. Sweating response to whole body heating was absent on limbs and trunk. In addition, plasma renin activity, and plasma and urinary aldosterone levels, failed to rise on tilting as well as after a low-sodium diuretic stimulation, suggesting the inability of autonomic nervous system to stimulate renin release by the kidney.

Indomethacin and propranolol were started at the same time. Indomethacin (25 mg three times daily) was given on account of its reported effect on postural hypotension, possibly due to inhibition of prostaglandin synthesis. According to Kochar and Itskovitz, an absolute or relative excess of vasodilator prostaglandin activity, particularly PGI2, has to be considered in Shy-Drager syndrome. The β-adrenergic blocking agent (propranolol, 40 mg daily, raised to 60 mg thereafter) was administered to lower the systo-diastolic hypertension, when reclining. After five days on full treatment, the patient could sit without change in blood pressure or orthostatic symptoms. One month later, she could walk with assistance because of slightly broad-based and ataxic gait. Her blood pressure ranged from 160/95 to 140/80 mm Hg, after treatment was started. Only one episode of orthostatic fall occurred 48 hours following reduction of indomethacin to 50 mg daily. Treatment with
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propranolol and indomethacin did not modify plasma renin activity or plasma aldosterone levels. Further repeated ECG monitoring of heart-rate variation in response to standing and during deep breathing showed unchanged values for both, R-R interval ratio at 30and at 15 beats, and E:I ratio, suggesting that the symptomatic relief of postural hypotension was not due to improvement of sympathetic function or enhanced renin formation. The patient is now in the 10th month of continuous therapy. No orthostatic falls have occurred, nor have further neurological signs developed.

In conclusion, although the mechanism by which indomethacin acts remains uncertain, we believe that it deserves a trial as an alternative approach to mineral corticoid treatment for the Shy-Drager syndrome. Combined treatment with a β-blocking agent also can be pursued in those rare cases where multiple system atrophy, autonomic failure due to central involvement, and severe supine systolic-diastolic hypotension occur. As far as we know, this is the first report where this drug combination has been used successfully.

GIULIANA GALASSI
Department of Neurology, University of Modena, Medical School, Modena, 41100, Italy

References


Is the “cerebellar” incoordination of Refsum’s disease due to structural lesions in the cerebellum?

SIR: Refsum’s disease is a recessively inherited disorder whose cardinal features are a chronic peripheral neuropathy, pigmentary retinitis and an excess of phytanic acid in various tissues and body fluid lipids.1 Likewise Charcot-Marie-Tooth disease is an inherited chronic peripheral neuropathy in which some patients have a disorder of movement similar to essential (familial) tremor.2

In Charcot-Marie-Tooth disease, if propractioceptive deafferentation is sufficiently marked, incoordination may occur. In other cases, however, incoordination (with or without wasting) mimicks cerebellar disease; this latter incoordination has been said to be due to various degrees of deafferentation and essential tremor.3 Harding and Thomas,4 when studying the clinical features of Charcot-Marie-Tooth disease assessed ataxia and tremor together because distinguishing between these two features separately often was difficult, a point recently emphasised in a survey of abnormal arm movements.6 Postmortem examination of patients with typical Charcot-Marie-Tooth disease showed that the cerebellum is normal; in none of the three cases with incoordination, categorised as cerebellar, that came to necropsy were the cerebellar systems abnormal.7 Patients with essential tremor may have incoordination mimicking cerebellar disease.8 This type of ataxia may be the most obvious manifestation of the disorder of movement for a period of time or may appear years after the onset of obvious essential tremor.9 Incoordination due to essential tremor affects more often the upper limbs alone, less frequently both the upper and the lower extremities together. It is interesting that in Refsum’s disease cerebellar incoordination used to be considered as a cardinal feature of the disorder. However, now that the disease is better understood, the cerebellar origin of the ataxia (which could not be explained in some cases on the basis of weakness and/or proprioceptive deafferentation) has been questioned.6 As Refsum pointed out in his review, incoordination is not present in some patients; when it is present, it may be reminiscent of that in cerebellar disease and is evident either in the upper limbs only or in all four extremities. Other patients with the disease have a disorder of movement similar to essential tremor (see among other cases his summary1 on the patients reported by Rake and Sanders and by Fryer et al.). It is worth noting that in the experience of the present author in patients with Charcot-Marie-Tooth disease associated with essential tremor, “cerebellar” incoordination may be absent,10 present in the upper limbs only,11 or present in all four limbs.12 Thus there seems to be a striking similarity in the manifestations and distribution of the “cerebellar” incoordination seen in patients with essential tremor, Refsum’s disease, and Charcot-Marie-Tooth disease associated with essential tremor, all of whom may exhibit either normal coordination, “cerebellar” incoordination in the upper limbs only or in all four limbs.

The site of the cerebellum as the cause of the “cerebellar” incoordination in Refsum’s disease may be seriously questioned for two reasons: (1) with the exception of some cases of cerebellar cortical atrophy in which incoordination predominates or is limited to the lower limbs and/or ataxia of gait, the incoordination in the spino-cerebellar degenerations affects equally the upper and the lower extremities. In Refsum’s disease the “cerebellar” ataxia may be limited, at least at one stage of the illness, to the upper extremities (see among other cases, the second patient reported by Gordon and Hudson;12) (2) in the spino-cerebellar degenerations presenting with incoordination there is damage to the cerebellum which is almost always more marked pathologically than suspected clinically, and which almost invariably can be seen by the naked eye. In contrast, as pointed out by Refsum,6 only five necropsy cases of Refsum’s disease have shown some microscopical changes in the cerebellum (see summary by Cammermeyer13). In this respect it has to be remembered that large parts of the cerebellum can be ablated without causing any cerebellar deficit.12 Furthermore some cases with Refsum’s disease show severe “cerebellar” incoordination in all four limbs with ataxia of gait without any pathological...