Unusual degenerative and environmental diseases seen in India

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Introduction

Degenerative diseases of the nervous system can rarely be attributed to a clear-cut etiologic or pathogenetic process. In India a specific hereditary spinocerebellar degenerative disorder is frequently observed with distinct clinical features being completely different from that seen in the West. Nutrition is one of the mainstays of the environment mankind lives in. Two diseases specific to tropical countries, in particular India, will be described namely:

1. malnutrition and it's effect on nervous system and
2. intoxication by consumption of the chickling pea, leading to the clinical picture of Lathyrismus.

No epidemiological survey of hereditary ataxias has been made in India, but hospital-based data and experience of seasoned neurologists leads one to believe that it is as prevalent as elsewhere in the world. However, there is one difference. There is a much greater prevalence in India of a variety of olivopontocerebellar degeneration (OPCD) which can be distinguished by slow saccadic eye movements and peripheral neuropathy.

Though MASS and SCHERER (19) described in 1933 an autopsy proven sporadic case of this variety from Germany, it was WADIA and SWAMI (29) from India who first drew attention in 1971 to the type-specificity, hereditary nature and greater prevalence of this disease in India. They had seen nine families since 1962. Autosomal dominant heredity was clearly established. Later WADIA et al. went on to report

1. the oculographic confirmation of the slow saccade (17),
2. the electromyographic and sural nerve biopsy evidence of peripheral neuropathy (for the first time in any variety of OPCD [29 - 31]),
3. the constant evidence of olivopontocerebellar and spinal cord degeneration in four autopsies (30, 32 - 34) and
4. the details of CT and MRI imaging during life (33, 34).

Further, specific degeneration of the neurones in the paramedian pontine reticular formation (PPRF) was shown to explain the saccadic slowing and the relative sparing of the flocculus of the cerebellum correlated with the relatively intact smooth pursuit eye movements (1, 2).
The former findings for the first time indicated the location of an anatomical substrate in humans for the “burst” and “pause” neurones, till then believed to be necessary for the generation of normal saccades only on experimental evidence in monkeys.

Between the reports of MASS and SCHERER (19) and WADIA and SWAMI (29) there was only one autopsy proven family, reported by SIGWALD et al. (23) from France. Though no oculographic record was made, the description of the eye movements and the autopsy left little doubt that it was the same disorder. GARCIN and MAN (11) also from France, described “viscous” voluntary eye movements in spinocerebellar degeneration of various types including FRIEDREICH’s ataxia, but not OPCD. However, in the absence of autopsy, the report remains incomplete. It is possible that from amongst the cases described by them as FRIEDREICH’s ataxia, some would have turned out at autopsy to be those of OPCD as in the well known Schut family. Finally, in 1967 KINI and VENUGOPAL (16) from South India reported a father and daughter with slow eye movements and commented that the clinical features “were compatible with a diagnosis of olivopontocerebellar degeneration”.

Subsequent reports usually of single families comparing them with those of WADIA and SWAMI attested to the global prevalence of this disease and its greater prevalence or recognition in India. Most of these have been summarized by WADIA earlier (32) and the subject reviewed thoroughly (33, 34). It is interesting that there is no similar sporadic case since MASS and SCHERER’s first account.

Clinical Features (Table 1)
The two consistently identifiable features are a progressive symmetrical cerebellar ataxia and slow voluntary (saccadic) eye movements. The abnormal tendon reflexes follow next. The patient presents with a steadily increasing gait disorder due to imbalance, followed by incoordination of limbs, intention tremor and dysarthria.

The patient makes no complaint and is unaware of the eye disorder which is a supranuclear ophtalmoplegia remarkable in that there is an increasing reduction in the velocity of the fast spontaneous and reflex induced (saccadic) eye movements, without a limitation in their range, at least until an advanced stage. The “viscous” eye movements are compensated by a characteristic jerking of the head to scan the surrounding, which an observant relative aware of the disease in his family may detect as an early sign. In the later stages, the eyes become more fixed, but can be still moved by reflex doll’s head manoeuvre, or caloric stimulation. There is no nystagmus, diplopia, squint or pupillary abnormalities. Conversely, the slow pursuit or tracking ocular movements are normal.

The tendon reflexes are often depressed, but may be brisk initially and later become absent. The plantar response may or may not be extensor. Dementia, involuntary movements like chorea, distal-limb wasting and impaired vibration and postural sensation in the lower limbs are seen in some patients. Even sub-clinical optic atrophy, myoclonus, macular degeneration, asymptomatic postural hypotension have been recorded in an individual family. The heart is normal and there are hardly any signs outside the nervous system. The ataxia and ophthalmoplegia worsen simultaneously, but in occasional families, one of them may be absent even till death.

The disease is essentially autosomal dominant and new mutation regularly occurs. The average age in the Indian patients was 27 to 28 years and life expectancy 13 years after recognition of the disease. It has been seen in all the three major communities of India, the Hindus, Muslims and Christians. Uncommon though elsewhere, it has been reported from many races, as also amongst the blacks and whites of USA and Canada (32 - 34).
TABLE 1
Clinical Features at initial examination of 40 Patients

<table>
<thead>
<tr>
<th>Signs</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar</td>
<td>40</td>
</tr>
<tr>
<td>Slow saccades</td>
<td>40</td>
</tr>
<tr>
<td>Tendon reflexes (Ankles jerk)</td>
<td>40</td>
</tr>
<tr>
<td>Absent/Depressed</td>
<td>24</td>
</tr>
<tr>
<td>Brisk</td>
<td>10</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
</tr>
<tr>
<td>Extensor Plantar</td>
<td>16</td>
</tr>
<tr>
<td>Posterior column signs</td>
<td>11</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>10</td>
</tr>
<tr>
<td>Wasted feet</td>
<td>7</td>
</tr>
<tr>
<td>Mental deterioration</td>
<td>5</td>
</tr>
<tr>
<td>Chorea</td>
<td>4</td>
</tr>
<tr>
<td>Wasted hands</td>
<td>2</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>2</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>4</td>
</tr>
<tr>
<td>Cataracts</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig. 1:
A close-up view of the posterior part of the base of the brain of a patient with OPCD and slow saccades showing an atrophic cerebellum and pons which is hardly visible. The medullary pyramids are prominent, but the olives cannot be seen.
Pathology

Autopsies have shown the disorder to be a variety of olivopontocerebellar degeneration (Fig. 1) with fall out of Purkinje’s and granular layer neurones, (more in the cerebellar hemispheres than in the flocculus), the pontine nuclei and the olives. Further, BUTTNER-ENNEVER et al. (1, 2), found on morphometry and enzymatic staining marked loss of large and medium-sized neurones in a restricted region of the PPRF close to the 6th nerve nucleus which are known to be homologous to the pre-motor saccadic burst and omni-pause neurones in the PPRF of the cat and monkey. This would somewhat explain the slowed saccades.

The posterior columns are maximally affected in the spinal cord, as a result of fall out of neurones in the posterior root ganglia. In a few patients, the anterior horn cell population has been reduced. In the peripheral nerves, there is fall out of the large and medium-sized myelinated fibres initially, and all sizes at a later stage.

Investigations

Investigations become necessary only in sporadic and early cases where some doubt arises regarding the diagnosis.

Oculography can record the slowed saccadic and normal velocity of the pursuit movements. Electromyography shows denervation in muscles, normal motor conduction velocity and absent or attenuated sensory action potentials even when the peripheral nervous system examination is normal.

Whilst CT and MRI of the brain of all patients with OPCD share some common features, some distinctions have been described (13, 33, 34). When done serially, they show the increasing degenerative atrophy of the pons and the cerebellum which begins in the anterior lobe of the vermis and later becomes pancerebellar, but sparing the flocculus at least till an advanced stage. Further, a distinctive inverted-molar-tooth image has been described by HUANG and PLAITAKIS (13). This results from atrophy of the middle and superior cerebellar peduncles and an ex-vacuo ballooning of the fourth ventricle due to an excavation of its floor (Figs. 2 and 3).

In summary, this variety of autosomal dominant cerebellar ataxia with slow voluntary eye movements and frequent lower sensory motor signs occurs in many races, religions and regions, but seems to be more prevalent or recognized in India.

Nutritional Disorders

Although malnutrition is still widespread especially amongst the children of India, systematic surveys of its effect on the nervous system are not available. It is interesting that conditions like Wernicke-Korsakoff’s syndrome, central pontine myelinolysis, Marchiafava-Bignami disease and cerebellar cortical degeneration described as common nutritional disorders mostly amongst Western alcoholics are rarely seen in India. SRINIVAS et al. (26) studying 100 adults of households earning less than US $ 45 per month, found 95% of them to be undernourished, their diet being inadequate in proteins, calories, iron and vitamin B complex. Anaemia, glossitis, oedema, underweight and anorexia were common, yet none had overt central or peripheral nervous system disease.

The identifiable groups of nervous system disorders due to malnutrition seen in India are

1. The vitamin B complex deficiency.
2. Vitamin D deficiency — osteomalacic myopathy.
3. Protein-calorie (energy) malnutrition.
Fig. 2: Axial CT scan through the upper pons showing ballooning of the fourth ventricle. The brachia conjunctiva (superior cerebellar peduncles) and tegumentum of the pons are diminished in size, especially posteriorly where the lateral aspects of the pons are flattened. The atrophic brain stem creates an inverted-molar-tooth image. The cerebellar atrophy is remarkable, the folia being widened and deepened.

Vitamin B complex deficiency

Amongst the neurological disorders resulting from vitamin B complex deficiency, pellagra remains the only clearly recognizable disease though it too is on the wane. Beri-beri or overt peripheral neuropathy due to vitamin B deficiency is now rarely seen.

Pellagra

In the sixties and seventies it was said (12) that “in Hyderabad (South India), 1% of admissions to a general hospital and in certain seasons 8 to 10% to a mental hospital are cases of pellagra”. A similar situation was seen in Rajasthan, north-west India too. Besides, diarrhoea, dementia and dermatosis, peripheral neuropathy, myelopathy and even amblyopia were reported, though there was some doubt whether these were due to lack of nicotinic acid or simply coincidental from other dietetic deficiency.

Electroencephalography was abnormal and revealed absent or irregular alpha rhythm, excess of theta activity, at times in bursts and even delta waves which rapidly reversed after a single injection of niacin as the patient improved clinically.

The disease occurs due to nicotinic acid deficiency. The poor villager subsists mainly on maize or millet jowar (sorghum) during the lean season. GOPALAN (12) believed that pellagra occurs due to an excess of leucine in both these staple crops, which causes an increase in the nicotinic acid requirement by interfering with the tryptophan and nicotinic acid metabolism. Additionally, in maize the tryptophan content is low and the nicotinic acid is bound and unavailable.
Fig. 3:
An axial section of MRI at the level of the uppermost part of the fourth ventricle shows:
  a) marked atrophy of the pons and brachia conjunctiva causing a molar-tooth effect
  b) atrophic anterior lobe of the cerebellum
  c) remarkably enlarged cisterns surrounding the atrophy.

Vitamin D Deficiency
Osteomalacia and proximal limb-girdle myopathy result from deficiency of vitamin D, due to undernourishment, multiple closely-spaced pregnancies with almost continuous lactation, and lack of sunlight especially in women of a certain community wearing the all-covering garment “the burkha”. The disease is therefore almost entirely in women.

Pains in the limbs, a waddling gait, difficulty in rising and exaggerated lordosis have been repeatedly well-recorded in the literature on nutritional osteomalacia since SCOTT’s graphic description of the disease from India in 1917 (7). X-rays of the pelvis, vertebrae and long bones of the limbs show classical changes of osteomalacia. EMG has shown evidence of a myopathy (14), which disappears rapidly along with clinical recovery on administration of vitamin D.

Protein-Energy (Calorie) Malnutrition
Kwashiorkor and marasmus are the names given to manifestations of extreme malnutrition resulting from low protein and calorie intake in infancy and childhood, but lesser forms of undernourishment also exist amongst the children of the so-called third world. Initially called as protein-calorie malnutrition (PCM) it is now customary to call it protein-energy malnutrition (PEM). The developing human brain is most vulnerable during the vital early rapid period of growth which begins in the 13th week of gestation and continues to the third or fourth year of life. It is during this period that myelination, dendritic arborization, synaptic connection and glial cell proliferation maximally occur. If significant PEM occurs during this period, not only is its effect immediate, but more ominously, persistent damage to the brain is believed to remain in those who manage to survive the initial deprivation (5, 6).
The acute effects

Besides the general features of Kwashiorkor, the immediate neurological effects are apathy, irritability, slow learning, generalized weakness, muscle wasting, hypotonia and areflexia. In some children, a waddling gait and proximal muscle weakness are more evident. Tremor and even upper motor neurone signs and autonomic dysfunction are occasionally seen.

Electroencephalography shows diffuse or focal delta waves on a disorganized background which can be reversed by proper nourishment. CT scan reveals cerebral atrophy in some. EMG and muscle biopsy show myopathic changes, and slow nerve conduction velocity has been recorded. Persistence of small diameter fibres indicating a delay in development of medium and large myelinated fibres has been found on sural nerve biopsy.

The delayed effects

The delayed or permanent defect which remains in children, who outlive the initial period of malnutrition are often subtle. These are not the result of gross anatomical anomaly or pathologically detectable destructive lesions, as seen for example in cerebral anoxia or hypoglycemia in infancy, but as functional disturbances of the brain from distortions and deficits in the ultimate mature brain due to “the dislodging of the intricate components of the growth program away from their delicately ordained interrelationshhip” (5, 6).

Much of the information has been gathered from animal experiment and observations, but many longitudinal studies on humans from India and elsewhere have been completed to test this belief (3, 4, 9, 27). CHAMPAKAM and others (3) in the Nutritional Research Laboratories, Hyderabad, India, saw several hundred cases of Kwashiorkor in a period over eight years, but observed 19 such children from the age of 18 to 36 months till they reached 8 to 11 years. They were regularly examined with specially modified tests to meet the needs of local culture and illiteracy, to assess their mental functions like reasoning, memory, perception, organization of knowledge etc. The final results were matched with controls amongst neighbouring children who were not nutritionally deprived but came from the same socio-economic background. The tests revealed that PEM had caused a significant disorder of mental function. GALLER et al. (9) carrying out a similar study found impairment of fine motor skill and coordination.

In 1976, JONES (15) mentioned that “ten million pre-school children are severely undernourished, 80 million are moderately undernourished and 130 - 160 million are experiencing undernutrition. Today, in 1990 as we approach the “health-for-all” year 2000, we are in no better position. It is said that even today, 150 million children under five are malnourished, 23 million severely so” (28), and PEM affects a quarter of the world’s children.

On the other hand, whilst stressing the major role of malnutrition, it has been pointed out that intelligent participation of parents in their child’s mental and physical growth cannot be underplayed. FRISCH (8) goes even so far as to say “surmises should not be treated as facts and millions of malnourished children should not be condemned as permanently retarded mentally”. In the balance, it appears that both factors play a role in the child’s ultimate mental development and capacity but the malnutrition factor is clearly more important. The vision of starving children is depressing enough, but the thought that millions will begin life with a built-in handicap is revolting and has very explosive social, political and economic overtones.

It will need all of universal man’s humanity, ingenuity and cooperation to solve this problem, even by early next century.
Lathyriasis

Lathyriasis known to be caused by consumption of the legume lathyrus sativus (chickling pea), has been endemic in central and north-east India for centuries and all attempts to banish it, have failed. Its prevalence in north-east India and Bangla Desh has been estimated as 0.3 to 2.5% of the population (18) and during famines, happily uncommon now in India, it can take on an epidemic proportion. Added to this are an unknown number of asymptomatic patients revealed on examination during prevalence surveys.

GANAPATHY and DWIVEDI (10) have reported that the disease is commoner in the male able-bodied Indian worker between 5 and 40 years. Females affected are usually between 6 to 20 years. The disease is often acute, the patient waking up with cramps, finds sudden weakness of the legs resulting even in a fall. Inclement weather and undue exertion can precipitate the paralysis. Less commonly the paralysis is subacute or chronically progressive. The disease is believed to be purely motor, but recently LUDOLPH et al. (18) have mentioned that 34% of their patients complained of paraesthesiae and perverse sensation in the legs at onset and 5.6% had urinary hesitancy.

On examination, signs of a spastic paraplegia have been found and depending on the severity and the support required in walking the patient’s disability has been graded as “no-stick”, “one-stick”, “two-stick” and “crawler” stages. Rarely mild spastic upper limb weakness has been detected. Recent clinical and neurophysiological studies quoted by SPENCER et al. and SPENCER and DASTUR (25) have indicated that a small proportion of severely affected patients can have mild, overt or covert toxic peripheral neuropathy or neuronopathy.

The disease usually affects poor, indigenous villagers, who have consumed chickling pea (Lathyrus sativus) which is locally called matri or kesari dal, all their lives as staple food or during the not uncommon emergency following floods or famines. However, 200 to 400 gms. of lathyrus sativus per day for one to three months or even shorter can also cause the disease (24). Some believe that sudden increase in the intake of the pea precipitates an acute attack. Then disease can regress if the consumption of pea is reduced or stopped early enough.

Credit goes to two groups of Indian scientists (20, 21) for independently identifying and isolating from the pea, the toxic compound beta-N-oxalyl amino alanine (BOAA), a free aminoacid as the toxic agent causing human lathrysm. An animal model has also been produced (24).

Scant neuropathological examination has shown degeneration of Betz cells and the anterior and dorsolateral corticospinal tracts in the thoracic, lumbar and sacral regions. SETHI et al. (22) mentioned that the chickling pea is still the third largest pulse crop in India and the reasons are not far to seek. It provides high quality proteins and carbohydrates, it is easy to cultivate, it is cheap. Besides, it grows rapidly, it is hardy and the cooked legume is tasty. In the absence of a cheaper source of food, the poor villager takes his chance, and attempts at eliminating the pulse have been repeatedly defeated due to economic and social factors and age-old habits. The race is, therefore, on for developing a safer strain, with low or no BOAA content, but with the taste and other qualities of the hardy chickling pea.

Summary

Amongst unusual degenerative disorders seen in India, a heredofamilial, autosomal dominant olivopontocerebellar degeneration with slow saccadic eye movements and peripheral neuropathy is most outstanding. It was first identified as a specific subtype
from India and its clearly greater prevalence was pointed out. A brief account is given here. Some observations on pellagra, osteomalacic myopathy, acute and delayed effects of protein-energy malnutrition and lathyriasis as common environmental disor-
ders are also made.

Key words
Olivopontocerebellar degeneration, slow-saccades, protein-energy malnutrition, pellagra, osteomalacic-myopathy, lathyriasis.

Zusammenfassung
Ungewöhnliche degenerative und umweltbedingte Krankheiten in Idien

Unter den seltenen degenerativen Erkrankungen, die in Indien beobachtet werden, ist
die hereditäre autosomal-dominante olivopontozerebelläre Degeneration, die mit lang-

Schlüsselwörter
Olivopontozerebelläre Degeneration, sakkadierende Augenbewegungen, Eiweiß-Ener-
gie-Mangelernährung, Pellagra, osteomalazische Myopathie, Lathyriasis.

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