Neuropsychiatric manifestations of chronic manganese poisoning

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Clinical manifestations appearing in labourers working with manganese in various industrial fields were discovered about 125 years ago. Couper in 1837 was the first to report the appearance of a peculiar neurological picture similar to Parkinson's shaking palsy in five men grinding manganese dioxide in France. Forty-two years later, Schlockow (1879) reported another 42 cases. In addition von Jaksch from 1901 to 1907 reported another 15 cases. Though he was the first to describe the peculiar 'cock walk' gait, yet he diagnosed them as having a disease similar to disseminated sclerosis. It was not until 1919 that the definite relation between the epidemiological, clinical, and pathological or toxic effects of manganese poisoning on the central nervous system was established by Edsall, Wilbur, and Drinker (1919). Their review drew attention to the serious effects on the central nervous system of this occupational disease. Subsequently a large number of cases have been reported from many countries. The first few cases in Egypt were described by Baader in 1932, and a few years later, in 1936, 26 cases were reported by Nazif and 11 cases by Scander and Sallam. Abd El Naby and Hassanein (1963), surveying chronic manganese intoxication from the industrial and hygienic points of view, commented on 32 cases with neuropsychiatric manifestations secondary to exposure to manganese ore in the mines. In this paper, another survey was done in which 13 further cases were added to the previous group, with the aim of studying and analysing the various clinical neuropsychiatric presentations of chronic manganese poisoning among Egyptians.

MATERIAL AND METHOD

This study was made on 45 male patients, ages ranging at the time of onset from 21 to 54 years with a median of 34 years (Fig. 1). Three of them were brothers and also cousins of a fourth patient. Another three cases were cousins. All the patients are inhabitants of El Khattara village and the surrounding district, Kous and Kef, near Luxor in upper Egypt. This area provides the main source of labourers for the manganese mines in the Sinai Desert at Abozeinama and Ombogma. They consist of two groups: the first began work in the mines at various intervals from 1925 to 1952, the second were working there after 1952 until 1963, i.e., after the introduction of wet drilling as a preventive measure and they were employed in various jobs there. It has to be stressed that the work in the mines was intermittent and each labourer used to work for only five months each year; they left work after the appearance of the signs and symptoms of toxicity.

Thirty-seven of them (82.2%) worked as dry-rock drillers, five (11.1%) as wet drillers, and only three (6.7%) as porters loading broken pieces of manganese ore. It is worth mentioning that even after using the wet drilling method in 1952, toxic manifestations appeared in four wet drillers.

Certain routine investigations were carried out in all the patients: e.g., urine and stools were analysed for manganese, and the blood picture, blood Wassermann reaction, and cerebrospinal fluid were examined, and radiographs were taken of the chest and long bones. All the results showed no abnormality. In addition 15 of them, who were severely incapacitated, were admitted to Kasr El Aini Hospital where they stayed for several months, and their clinical manifestations were followed up. Further laboratory investigations were carried out, including liver function tests, liver biopsy, glucose tolerance.

![FIG. 1. Age distribution at time of onset of manganese poisoning in 45 cases.](http://jnnp.bmj.com/ on August 13, 2017 - Published by group.bmj.com)
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DURATION OF EXPOSURE TO MANGANESE. The period of exposure before the appearance of the manifestations of toxicity was not constant (Table I). The shortest was five months and the longest was 25 years with a median of nine years.

<table>
<thead>
<tr>
<th>DURATION OF EXPOSURE TO MANGANESE</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4 months</td>
<td>4</td>
</tr>
<tr>
<td>1-5 months</td>
<td>2, 8, 11</td>
</tr>
<tr>
<td>5-10 months</td>
<td>10</td>
</tr>
<tr>
<td>10-20 months</td>
<td>4, 6</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
</tr>
</tbody>
</table>

MODE OF ONSET. The onset of clinical symptoms was acute in 13 cases and insidious in the remaining 32 (Table II). In those of acute onset, the initial symptoms were neurological in seven cases and in five took the form of a psychiatric disturbance. In only one case were there constitutional symptoms in the form of fever and rigors. The symptoms of those of insidious onset were variable. Seventeen cases presented with neurological disturbances, 11 with neuropsychiatric signs and symptoms, and in the remaining four there were psychiatric symptoms in the form of mental fatigue, retardation of thought process, and lack of concentration.

<table>
<thead>
<tr>
<th>MODE OF ONSET IN 45 CASES OF CHRONIC MANGANESE POISONING</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Neurological</td>
<td>1, 7</td>
</tr>
<tr>
<td>Acute Psychological</td>
<td>9, 13</td>
</tr>
<tr>
<td>Acute Constitutional (fever and rigors)</td>
<td>1</td>
</tr>
<tr>
<td>Insidious Neurological</td>
<td>17, 45</td>
</tr>
<tr>
<td>Insidious Psychological</td>
<td>4, 32</td>
</tr>
<tr>
<td>Insidious Combined</td>
<td>11, 45</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
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INITIAL SYMPTOMS. Table III summarizes the data of the initial symptoms of the whole group, and it may be noticed that they were multiple and of varying combinations. Since the data in 41 cases are retrospective, it may be subject to the discrepancies of such a study, especially in view of the long period which elapsed between the appearance of the initial symptoms and the time of examination in 1963.

<table>
<thead>
<tr>
<th>TABLE III</th>
<th>INITIAL SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Exhaustion syndrome</td>
<td></td>
</tr>
<tr>
<td>Weakness of extremities</td>
<td></td>
</tr>
<tr>
<td>Inability to walk without support</td>
<td>26</td>
</tr>
<tr>
<td>Bedridden</td>
<td>3</td>
</tr>
<tr>
<td>Subjective sensory disturbances</td>
<td>5</td>
</tr>
<tr>
<td>Tremors</td>
<td>9</td>
</tr>
<tr>
<td>Oculogyric crisis</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>30</td>
</tr>
<tr>
<td>Hypersonnia</td>
<td>7</td>
</tr>
<tr>
<td>Lethargy</td>
<td>45</td>
</tr>
<tr>
<td>Inverted sleep rhythm</td>
<td>3</td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
</tr>
<tr>
<td>Acute psychosis</td>
<td>5</td>
</tr>
<tr>
<td>Mild psychotonic disturbances</td>
<td>22</td>
</tr>
<tr>
<td>Disposition</td>
<td></td>
</tr>
<tr>
<td>Spontaneous laughter</td>
<td>15</td>
</tr>
<tr>
<td>Spontaneous crying</td>
<td>3</td>
</tr>
</tbody>
</table>

It is interesting to report that those cases of insidious onset gave the history of generalized weakness, langour, and of being easily fatigued on exertion, which is a picture simulating the exhaustion syndrome of myasthenia gravis. These were some of the earliest symptoms and invariably preceded any others.

Twenty-five patients complained of weakness and marked stiffness of the limbs, especially the calves of the legs with mild cramp-like pains on walking, and later they were unable to walk without support. In addition they showed propulsion, retropulsion and lateropulsion. In another three, these disabilities were sufficiently incapacitating for the patients to become bedridden.

In only eight patients was there an early complaint of a marked tremor of the extremities leading to clumsiness in the use of hands and legs. This was associated with involuntary nodding of the head and neck. In only one case, however, were there frequent attacks of oculogyric crises early in the onset of the disease.

Nearly all of them gave a history of sleep disturbances; 30 reported insomnia, seven diurnal hypersomnia, and five lethargy. Only three showed a definite history of inverted sleep rhythm.

In five patients, there were definite subjective sensory disturbances. All had distressing paraesthesiae in all four limbs; in one case the face was involved and in two others severe, spontaneous cramp-like pains occurred in the calf muscles, especially at night.
Among the acute psychotic disturbances, two of the patients became severely excited, agitated, hallucinated and deluded, necessitating admission to the Abbassiah Mental Hospital as they became unmanageable. However, their mental condition improved after a few weeks. The outstanding history from the other three cases was one of emotional instability, irritability, various behaviour disorders, insomnia, and occasional refusal of food. Mild psychotic disturbances of insidious onset were reported by 22 patients or by their relatives during the early stage of the disease. They were irritable with a slight change in mood, conduct, and behaviour and in some, an occasional period of confusion. Spontaneous, incongruous laughter was reported by 15 of these patients, and spontaneous crying by three. The psychiatric symptoms invariably regressed while the neurological ones became either stationary or showed gradual progress, culminating in the various full-blown clinical pictures which will be discussed later.

PRESENTING SIGNS AND SYMPTOMS  At the time of examination, the presenting signs and symptoms were a combination of neurological, neurovegetative, and psychiatric features (Tables IV, V, VI). For simplicity and clarity, our case material will be classified in three main groups according to the clinical findings.

Group I  In this 29 cases (64.4%) presented with extrapyramidal manifestations (Table IV); group II, 10 cases (22.2%), presented with combined extrapyramidal and pyramidal manifestations; group III, six cases (13.4%), presenting with extrapyramidal, pyramidal, and cerebellar manifestations, i.e., disseminated or systemic syndrome.

Group I  Most of the patients in this group exhibited a syndrome in which tremors, rigidity, facial immobility and loss of associated movements were dominant. This group presented abnormal involuntary movements, either tremor or athetoid movements being present in all the cases, but differing in distribution and sequence. The lips and tongue were by far the most constant sites for static tremors which were fine and rhythmic but ceased during sleep. Less frequently affected were the extremities, neck, and lower jaw muscles. Tremors of the extremities were present in 21 cases and involved mainly the hands and fingers, especially when fully extended. Those of the neck muscles were characterized by alternating flexion and extension of the head which appeared in three patients and by lateral rotation in another one. In three cases the type of tremor affected the lower jaw causing the mouth to open and close or to move laterally from one side to the other. In only one case did the tremor resemble the 'pill rolling' movements of paralysis agitans, being more marked in the right hand than the left. The metacarpo-phalangeal joints were flexed, but the interphalangeal joints were extended. In another case, slight athetoid movements involving both hands and wrists were present.

Dyskinetic features were minimal and localized in this group but in four cases there were tonic
spasms in the facial and neck muscles. One patient (Fig. 2) had grimacing movements amounting to risus sardonicus affecting the facial, platysma, and neck muscles. In two others the sternomastoid muscles were mainly involved leading to mild, spasmodic torticollis. The fourth case had occasional, spasmodic, tonic flexion at the elbows and hands. In none of these cases were the trunk muscles affected.

All the patients in this group presented with slowness in initiating and maintaining movements, lack of spontaneity and marked reduction in frequency and range of both voluntary and involuntary movements. The classical mask-like Parkinsonian facies, with increased sebaceous secretion, was evident in 23 cases.

Muscular rigidity, equally involving agonist and antagonist groups leading to cog-wheel rigidity, and especially affecting the trunk and lower limbs, was evident in all the cases. In 26 of these it gave rise to a general attitude of flexion (Fig. 3a) and in the remaining three to an attitude of extension (Fig. 3b).

The 'cock-walk' gait of von Jakusch with talipes equinus or equinovarus and the characteristic tendency to walk on the metatarso-phalangeal joints was a striking feature in 17 cases. It was bilateral in 11 (Fig. 3c) and unilateral in the remaining six cases (Fig. 3d).

A festinant gait was seen in eight cases and the patients appeared to be rooted to the ground on walking. The phenomena of propulsion, retropulsion, and lateropulsion were present in all the patients of this group but propulsion was the commonest.

Other neurological findings were: the tendon jerks were normal in 21 cases, exaggerated in six, and diminished in the remaining two. The hyperreflexia differed in distribution in being generalized in both upper and lower limbs in four cases; in three of them there was evidence of both cervical and lumbar spondylisis and in the fourth a pellagrous rash was present on the face, extremities, and pressure points. The hyperreflexia was localized in the lower limbs in another two patients; in one, both the knee and ankle jerks were exaggerated, and in the other, only the ankles.

On the other hand, in the two patients showing a hyporeflexia it was generalized in one, while in the other it was limited to the knees and ankles and this patient had a history of laminectomy for prolapsed disc and the operation scar was apparent on his back.

As regards the superficial reflexes, the plantar response was flexor in the whole group, and the abdominals were also intact.

All types of sense modalities, whether deep or superficial, were normal in 24 cases, while in the remaining five, there were sensory changes of different distributions. It was of the peripheral neuritic type in the pellagrous patient, of the radicular type in the case with laminectomy, and irregular in the spondylitic cases.

Though sphincter disturbances were absent, seven patients complained of weakness of libido. In only two cases were there disturbances of lateral conjugate movements and accommodation-convergence reflexes of the eyes. In the remaining cases all the cranial nerves were intact and the fundi were normal.

Group II This group showed extrapyramidal manifestations similar to those previously described
in group I, but they were associated with definite signs of pyramidal involvement in varying degrees and combinations. In all the patients of this group, the hyperkinetic signs were relatively minimal and none of them showed any dyskinetic disturbance. In all the cases, weakness of the pyramidal distribution could be demonstrated. It was more marked distally than proximally, involving the extensor muscles of the upper limbs more than the flexors but the reverse in the lower limbs. The weakness was bilateral and symmetrical in all cases except one in which it was right sided and of a hemiplegic distribution.

All the cases presented a mixture of hypertonia and spasticity. The deep tendon jerks in both upper and lower limbs were exaggerated. Ankle clonus was present bilaterally in two cases, and unilaterally in two others. The abdominal reflexes were absent in six out of the 10 cases. The plantar response was extensor bilaterally in six, unilaterally in one, and equivocal in the remaining three.

In contradistinction to the previous group, sphincteric disturbances in the form of precipitancy of micturition and constipation were present in seven cases. The gait was of the von Jaksch's type on both sides in five patients and unilateral, with right talipes equinovarus in another one, spastic and shuffling in another three. The remaining two patients were bedridden, one being completely paraplegic and the other quadriplegic (Fig. 3e). Sensation was normal in eight cases, and affected in the remaining two. The hemiplegic patient had right-sided hypoesthesia and the paraplegic one had glove and stocking hypoaesthesia.

The cranial nerves were unaffected except in the hemiplegic patient, who had right-sided upper motor neurone affection of the right seventh and twelfth nerve. The fundi were normal except in this last patient who had evidence of retinal and peripheral atheromatous vascular disease and had been hypertensive for a long period.

**Group III** Clinical examination of this group showed the presence of cerebellar deficit in addition to extrapyramidal and pyramidal signs in five patients while the remaining case showed a combination of extrapyramidal and cerebellar dysfunction only.

In all these cases there were gross kinetic intention-type tremors with dysmetria in the extremities, and dysdiadochokinesis was observed in the upper limbs of three cases. Speech was staccato in three, monotonous in two, and slow in the remaining one. The deep tendon jerks were exaggerated in five patients. Ankle clonus was elicited in two patients. The plantar response was bilaterally extensor in one case, unilateral in another, equivocal in two, and normal in the remainder. While the abdominal reflexes were diminished in two and present in the remaining four cases, the gait was wide based of the cerebellar type in all cases. None of them showed nystagmus or any other cranial nerve affection. All sense modalities whether superficial or deep were intact in all the patients.

**DISCUSSION**

Our group of 45 labourers, showing the various neuropsychiatric manifestations of chronic manganese poisoning, is one of the largest that has been reported. They were affected while working in the various processes of extraction of the black dioxide of manganese (pyrolusite), either during mining, grinding, sorting, packing, or loading the ore.

According to the records of the Egyptian Ministry of Public Health and Ministry of Labour, the total number of workers in the mines of Abo-Zeinema and Om-Bogma was only about 500 till 1952 and it increased to 1,850 in 1962. The total number of the reported cases of chronic manganism in the U.A.R., including our material, does not exceed 75 persons. Even if we make allowance for those patients who have been missed or wrongly diagnosed, it would appear that this type of poisoning is still a rarity in this country.

However, its incidence appears to be relatively high compared with that in other countries. This can be easily explained if the method of extraction of the ore is considered. During the period between 1925 and 1952, the process of extraction of the manganese ore was by dry rock drilling where no prophylactic hygienic measures were undertaken and during this period 41 of our cases developed toxic manifestations. After the use of wet rock drilling with proper ventilation, only four workers became affected. Nevertheless the factors which may be responsible for the appearance of the toxic manifestations are difficult to explain. However, at least two factors may play a role in our material: first there may be a special susceptibility or vulnerability of the central nervous system in certain persons. Secondly, the degree of concentration of the manganese dust in the atmosphere is likely to be important, since the main route of absorption is through the lungs rather than from the digestive tract. In favour of the first factor is the fact that 15-5% of our cases were brothers or cousins, that only a very small percentage of the labourers developed the toxic manifestations though they were working under the same conditions, and that the duration of exposure to manganese is very variable, ranging from five months up to 25 years. It may be that the more vulnerable
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persons developed the signs and symptoms after a relatively short period.

The significance of the second factor can be shown clearly from the incidence of manganism in the various jobs. While it is highest (80-2%) in the dry drillers who worked in the dusty atmosphere of the underground galleries, it is lowest in porters (67%) loading and unloading the ore in the open air. In addition, the marked change in the incidence of chronic manganism that occurred in our series is worth mentioning. Before 1952, about 14% of the labourers developed the toxic manifestations, but when wet rock drilling under adequate ventilation was used the percentage dropped to about 0-2.

These findings are in accordance with those of other authors (Flinn, Neal, Reinhart, Dallavalle, Fulton, and Dooley, 1940). In addition Freise (1932) and Bubarev (1931) could not find any neurological manifestations in an extensive study of manganese loaders. Similarly, Baader (1932a and b) reported such manifestations in only one porter among all porters unloading manganese ore in the harbour of Hamburg.

In order to throw some light on the pathogenesis and to explain the variability of the symptoms and clinical pictures of the neuropsychiatric manifestations in chronic manganese poisoning, we must survey the few pathological reports of other authors on necropsies (Ashizawa, 1927; Trendtel, 1936) and in experimental monkeys (Mella, 1924).

The essential and characteristic lesion, common in all the necropsies and experimental animals, is destruction of the ganglion cells of the basal ganglia. Ashizawa found histopathological changes in the pons, the internal capsule and the cerebral peduncle. Trendtel reported degeneration and gliosis in the corpus striatum, in addition to a decreased number of neurones in the putamen and globus pallidus. He likewise found the same kind of changes in other parts of the brain.

Canavan, Cobb, and Drinker (1934) described the pathological changes in a manganese worker who died after 14 years of disability from manganese poisoning. There was atrophy of the cerebral cortex, especially in the frontal lobes and in the cerebellum, but the main changes were in the basal ganglia which were shrunken and distorted. Histopathological studies revealed gliosis and degeneration of the nerve cells, particularly in the optic thalamus, globus pallidus, lentiform nucleus, caudate nucleus, and the putamen.

On the whole, the clinical and pathological picture of manganese poisoning points to involvement of the basal ganglia, sometimes of the globus pallidus and frequently of other parts of the nervous system such as the pyramidal system, cerebellum, and its connexions. But they are not consistently affected to the same extent, hence the variability from one group of cases to another.

The high incidence of acute onset in our cases (28-9%) has never been reported before, since the most commonly reported mode of onset was insidious (McCrae, 1925; von Jakob, 1901).

In none of the previous reports were the clinical manifestations of cerebellar deficit so marked as in our third group, constituting 13-4% of the cases.

Although Loebe (1936) attributes the von Jaksch's gait to cerebellar dysmetria, in none of our cases was it associated with clinical evidence of cerebellar affection. On the contrary this gait results from marked rigidity in the lower limbs unequally affecting the agonists and antagonists and it is similar to what occurs in decerebrate rigidity.

But on the whole, our results conform with those previously reported (McNally, 1935).

SUMMARY AND CONCLUSIONS

Forty-five cases of manganese poisoning are reported. Neuropsychiatric symptoms had developed from five months to 25 years after the onset of exposure to manganese.

An insidious onset with fatigue and langour was commonly observed, and this proceeded to weakness and stiffness of the gait, and disturbances of balance of the type observed in Parkinsonism.

In 50% of the cases von Jaksch type of gait appeared. The motor signs might be purely extrapyramidal or pyramidal or cerebellar, or a mixture of these. Marked emotional and neurovegetative disturbances were observed.

To conclude, chronic manganese poisoning is a crippling disease with permanent disabilities, especially in regard to the use of the lower limbs. None of our cases showed any improvement after being removed from the mines; on the contrary, in all of them, the neurological disabilities progressed and only the psychic changes regressed.

REFERENCES


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