Syndrome Neuro-Végétatif Malin

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INTRODUCTION

Shortly after the introduction of the neuroleptica into psychiatric practice in 1952 as a therapeutic means of salient potential usefulness, reports appeared in French literature on a syndrome which comprised a fever and the symptoms of extrapyramidal disease such as akinesia, mutism and muscular rigidity in association with severe symptoms of autonomic nerve involvement and which proved fatal not infrequently.[1-14]

Furthermore, reports of serious complications of therapy with similar psychopharmacologic agents were made in succession from the American Continent since the latter half of the year 1950.[15-20] Nowadays such adverse reactions with neuroleptic medication are being described as "syndrome (neuro-végétatif) malin".

In Japan, there has recently been a growing interest aroused in syndrome malin. Nevertheless, it seems that this syndrome not infrequently is mistaken for or treated erroneously as "akute tödliche Katatonie" or encephalitis. In 1974, 9 cases of the syndrome were first reported by Otsuka et al[21]. and subsequently, in 1976, additional 4 and 5 cases, respectively, were reported by Ikeda et al.[22] and Ito et al.[23] Serious attention has thus come to be focused on this pathological entity. The purpose of this paper is to present 3 cases presumably of syndrome malin experienced by us in recent years.

CASE REPORTS

Case 1: a 19-year-old women's college student

The family history and the history of inheritance revealed nothing remarkable, nor had there been any significant disease in the past. Her

birth was normal. The onset of disease occurred when she was 19 years old with a clinical picture of catatonic excitement. There was a gradual worsening of symptoms, such as desultory thought, psychomotor excitement, monologue, negativism and stereotypy, with which she was hospitalized.

Examination on admission revealed neither somatic abnormalities nor neurological defects.

Immediately after hospitalization the patient was given haloperidol, 5 mg intramuscularly. Three hours later she became less excited and took a small amount of meal with other patients. In the evening of that day she was again in a state of pronounced psychomotor excitement, for which a compound injection of 50 mg chlorpromazine and 50 mg promethazine (Cocktelin H®) was administered intramuscularly. At the same time she was started on a combined daily oral regimen of 75 mg chlorpromazine, 100 mg levomepromazine and 50 mg promethazine.

At the 3rd day of initiating this oral medication, at least in our eyes, she looked cheerful and was self-composed enough to cooperate with her attending physician during a psychiatric interview and examination. But in the afternoon of that day she began to develop muscular rigidity, tachycardia, akinesia, dysphagia and changes in blood pressure. Hence the neuroleptic medication was suspended and parenteral fluid infusion was instituted. At that time her pupils were constricted and the light reflex was minimal. On the 4th day she fell in a precomatose state, presenting with cyanosis, profuse sweating, salivation and urinary incontinence. Following these symptoms a high fever of above 40°C set in, which further rose to 41°C on the following day. Antipyretics proved to be entirely ineffective. Moist rales were heard over the lower portion of the left lung, where a shadow suggestive of bronchopneumonia was seen on x-ray. Significant laboratory findings were neutrophilia (9600) with associated shift to the left; A/G ratio, 0.88; GPT, 40 units; otherwise there were no abnormalities. Serum electrolytes were within the normal range. On the 7th day of her hospitalization the pneumonia subsided but a high fever (above 40°C) and sinus tachycardia (more than 120 beats per minute) were still present. Moreover, a stuporous state, salivation, gross fluctuations of blood pressure and cyanosis persisted. On the 8th day generalized convulsions occurred. The beta-blocker proved to be effective, though transiently, in the control of tachycardia. LE cell (−), CRP (−), cerebrospinal fluid findings (−). On the 11th day of hospitalization she developed acute cardiac failure; peritoneal irrigation was started at once and at the same time intensive parenteral fluid infusion was given. Unfortunately, however, the digestive tract began to

bleed and her general condition turned for the worse progressively. She died of cardiac failure on the 28th day of her hospital stay. Autopsy was not feasible.

Case 2: a 22-year-old jobless man

The patient's family history was not remarkable and there was no hereditary predisposition. Since his early childhood he had a slight mental retardation. At his age of 16 he began to develop a tendency to autism. He would be speechless with his friends; showing bizarre behaviors, such as whispering to himself, giggling and crookedness, rather prominently. He often stayed away from school and nonsensical behaviors came to the fore in his activities of daily living. After graduating from middle school he wouldn't seek a job and he tended to confine himself to his room. With these symptoms he was taken to a mental hospital for psychiatric evaluation when he was 18 years old and was immediately hospitalized under the diagnosis of chronic schizophrenia associated with mental subnormality. He was given psychotropic drug therapy without any evidence of improvement.

In July, at his age of 21, he was on a daily oral drug regimen of 9 mg haloperidol, 150 mg chlorpromazine, 75 mg levomepromazine and 50 mg promethazine. However, because of his frequent refusal to take these medicines, 1 g of fluphenazine enanthate was injected into his gluteal muscles. On the 3rd day after fluphenazine injection his salivation, muscular rigidity, intention tremor, tachycardia and drowsiness became increasingly manifest. On the 5th day akinesia, a fever of 38–39°C and excessive sweating supervened and fluctuations of blood pressure became strikingly clear. Hence the psychotropic medication was discontinued to be replaced by intensive parenteral fluid infusion. Despite all this, however, his consciousness became progressively worsened from drowsiness to precoma and further to coma; the heart rate and the frequency of respiration increased to 145/min. and 32/min. respectively and the body temperature elevated to above 39°C. At that time the laboratory study demonstrated a leukocyte count of 9550 with a shift to the left; NPN, 39 mg/dl; urea N, 22 mg/dl; LAP, 250 u.; LDH, 1.146 u.; GOT, 52 u.; GPT, 49 u.; serum electrolytes were within normal limits. An intravenous beta-blocker proved effective, though transiently, in the control of tachycardia; cryotherapy produced a favorable effect on fervescence but antipyretics all proved of no value at all. A reddened skin area in the sacral region turned rapidly to vesicles which in turn developed into a decubitus ulcer. Two weeks after the appearance of the prodromal symptoms the patient's general condition began to improve

and he now was able to take food, though small in amount, with assistance. Since, however, he still refused to take a meal at times and exhibited spells of excitement, medication with chlorpromazine, 25 mg once daily intramuscularly, was started. He became free from psychomotor excitement and his general condition also showed some signs of gradual improvement. Weight loss during this 2-week period amounted to 7 kg.

In this case, the patient continued to exhibit manifestations of oral dyskinesia, e.g. rolling the tongue awkwardly and protruding the tongue, and queer bodily movements, e.g. trembling the whole body with legs stretched against the floor, for 3 months even after the syndrome malin had disappeared. Thereafter he became reasonably free from psychic symptoms and communicative enough to enter into an interpersonal relationship though to a slight degree.

Case 3: a 20-year-old jobless woman

The family history and the history of hereditary disease revealed nothing remarkable. During her primary school days she was a bright and cheerful girl with a good school performance. But later in her middle-school days she was reluctant to attend school, became gradually close-mouthed and gloomy and made poor school records. When she was a third-year middle school girl, she was institutionalized at a mental hospital for one year. Some time after remission was achieved, the symptoms recurred, for the treatment of which she was hospitalized for another 3 months. Soon after entering a women's college her condition became noticeably worsened; in March, at her age of 20 years, she began to demonstrate silly acts, such as giggling, standing still in the vestibule of her house with a broom at hand, leaving a tap open and lighting letters and newspapers in her room, hence she was hospitalized once again. At the time of her hospitalization auditory hallucination, delusion of persecution, giggling and grimacing were noted. Therapy was started with the daily oral administration of 4.5 mg haloperidol, 75 mg levomepromazine and 75 mg promethazine. In the 3rd month of her hospital stay her condition improved to a reasonable extent. At that time she underwent operation for hypertrophic rhinitis and the recovery was uneventful. At the 3rd week after operation she began to exhibit sinus tachycardia (130 beats/min.) associated with muscular atrophy, tremor, fever (38°C level) and drowsiness. Although no abnormalities were noted on liver and renal function tests as well as in serum electrolytes with the only exception of a leukocyte count of 6700, the psychotropic medication was withdrawn and parenteral fluid infusion was initiated. Her blood pressure was quite unstable and tachycardia and salivation were still persisting. Moreover, she fell in a precomatose state in the wake of a

continuous high fever of 40°C on the 7th day after the appearance of the premonitory symptoms. Moist rales were audible over a lower portion of the lungs; chest x-ray provided evidence of pneumonia in the same regions. Antibiotic medication was started. At that time there was overt leukocytosis (17,500) with associated shift to the left. Ten days later, pulmonary lesions were resolved and at the same time her psychic manifestations improved. She lost 5 kg of weight during these periods. To be noted is our impression that adrenocortical hormone, 20 mg per day, proved beneficial in the abatement of the high fever.

DISCUSSION

The syndrome neuro-végétatif malin, a pathological condition produced by the use of the neuroleptica, has the following characteristic features: it is preceded or heralded by specific prodromal symptoms which comprise psychoneurologic manifestations, e.g. severe muscular rigidity, mutism, akinesia or violent excitement and dysphagia, and manifestations of autonomic nerve involvement, such as tachycardia, excessive sweating, hypersecretion and fervescence, irrespective of the type of neuroleptic drug used and its dosage level. This set of symptoms is considered as representing an intensified form of the so-called "signes d'impregnation". Unless adequate measures are taken at this stage, a high fever of 40–41°C occurs within 24 to 48 hours; worsening of the prodromal symptoms and of disturbance of consciousness (from lethargy to precoma and finally coma) and intense blood pressure changes ensue and may eventuate in the patient's death in a state of high fever and facial pallor.

These symptoms are known to be analogous or related to those of heat stroke[19], "akute tödliche Katatonie[24]", exhaustion syndrome[25], catatonie pernicieuse or délire aigu, but are differentiated from the latter conditions by a causal relationship between neuroleptic medication and the occurrence of the symptoms, especially the reproducibility of neurolepticainduced symptoms. Furthermore, the conditions enumerated above are also said to be dissimilar to the syndrome in question in that they are rarely associated with symptoms of extrapyramidal disease and normally accompanied by akinesia and mutism in the presence of fever.

Clinical manifestations common to our 3 cases are neuropsychiatric symptoms, e.g. muscular rigidity, tremor, akinesia, mutism and a lowering of the level of consciousness from drowsiness to precoma and finally to coma, symptoms of autonomic nerve involvement, e.g. tachycardia, excessive sweating, salivation and fluctuations of blood pressure, and other additional symptoms of urinary incontinence, decubitus ulcer and so

forth. These symptoms all manifest themselves, to more or less extent, as premonitory ones and then rapidly become worse as a fever of around 40°C develops. This fervescence was entirely unresponsive to antipyretic medication, while it responded to some minor extent to adrenocortical hormone in one of the present 3 cases. It seems rather that a more reliable temperature-lowering effect may be expected by the use of ice bags applied to the axilla, femoral region and lateral side of the neck bilaterally. A similar measure was already recommended by Ito et. al[23]. Persistence of a fever exceeding 40°C for a few days or even longer might be regarded as a sign of poor prognosis.

On physical examination bronchial hypersecretion, frequent productive cough, stridor, tachypnea and tachycardia are usually noted. The concurrence of dysphagia with these symptoms predisposes the patient to bronchopneumonia. In Cases 1 and 3, there was unquestionable evidence of pneumonia noted on chest x-ray, nevertheless, no distinct parallelism was observed between x-ray findings and the course of fervescence of syndrome malin.

Neurologically, pathological reflexes, abnormalities of physiological reflexes and symptoms of meningeal irritation were totally absent, however. In one of our present cases (Case 3), tremors subsided as the bod temperature declined, while muscular rigidity persisted to the end, dyskinesia only being demonstrable for several months.

Turning to clinical laboratory findings, sinus tachycardia was noted on ECG in all the 3 cases, and an intravenous beta-blocker was found effective in abolishing or reducing this sign even though transiently. Invariably in all cases the leukocyte count was increased and the differential hemogram showed a shift to the left. The A/G ratio was decreased, NPN or urea N, on the other hand, was elevated, GPT and GOT elevated, and likewise LAP and LDH elevated; these changes, however, seemed to be reversible and of a transient duration. In Case 1, abnormal values for serum electrolytes were observed after the development of acute renal failure, whereas prior to this stage no departure from normal of serum electrolytes, particularly potassium, was demonstrable. Ikeda et al[22]. and Ito et al[23]. paid attention to changes in CPK. Unfortunately, however, no measurements were made of CPK in our present cases.

The cerebrospinal fluid was free from abnormalities in all 3 cases. Neither abnormal discharges nor left-to-right difference in pattern were noted on EEG, although some minor degree of slowing of activities was observed.

The facts that all the 3 patients were invariably aged around 20

years and that there was a moderate degree of mental subnormality (Case 2) strongly suggest that the condition under investigation is associated with some fragility of the central nervous system[4,10,12,17,19,22]. It seems quite likely that such a defect, when combined with a debility due to continuous and persistent refusal to take food and long-sustained insomnia as well as a high temperature and high humidity of summer in Japan, leads to a predisposition to syndrome malin, as was the case with Cases 2 and 3.

The dosage of the neuroleptica employed in our cases may not be considered as overly high since it conforms with the current practice of this kind of drug therapy. However, it seems unquestionable at least that these drugs are more likely to cause syndrome malin when they are administered orally than when used parenterally[3,4,5,12,21,22].

Reported cases of syndrome malin due to long-acting neuroleptica, such as fluphenazine enanthate, have been rapidly increasing in number particularly since 1970. Ample caution should therefore be exercised in using this type of neuroleptics.

Haloperidol[4,5,6,12], levomepromazine[1] and chlorpromazine[18] were also shown to have caused syndrome malin. In Case 1, a mixture of chlorpromazine and promethazine was used. In Case 2, on the other hand, the use of chlorpromazine brought about an improvement of the condition and this is quite in agreement with a report of Deniker et al[26].

The true pathogenesis of this particular condition is still obscure. Of great interest is the fact that symptoms observed in malignant hyperthermia during anesthesia[27,28,29,30,31] bear a close resemblance to those of syndrome malin.

Ikeda et al.[22] stressed a possible relationship between elevated CPK and syndrome malin. This issue remains to be settled by further studies, since there are reports stating that acute psychosis is associated with an elevation of CPK.

SUMMARY

Three cases of presumed syndrome malin caused by neuroleptic medication were presented. These patients were all juvenile, aged around 20 years, with one of them having mental subnormality. These findings strongly suggest fragility somewhere in the central nervous system. It seems also quite likely that a debility resulting from refusal to take food, insomnia and psychomotor excitement and unfavorable climatic

conditions (e.g. high temperature and high humidity) might play a major role in the causation of syndrome malin.

Our present cases point to the possibility that the use of haloperidol, levomepromazine, chlorpromazine, fluphenazine enanthate or a combination of chlorpromazine and promethazine, among other neuroleptic drugs currently available, might be implicated as a causative agent. In this connection, it is interesting to note that medication with chlorpromazine brought about a symptomatic remission in one of our cases.

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