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ORIGINAL PAPER

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Neuroleptic malignant syndrome in a 4-year-old girl associated with alimemazine

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Abstract Neuroleptic malignant syndrome (NMS) is a rare but serious disorder caused by antipsychotic medication including phenothiazines. For sedative purposes, increasing doses of alimemazine were administered to a 4-year-old multiple handicapped girl, with cerebral damage of the basal ganglia. She developed extra-pyramidal motor disturbances, an autonomic disorder, lowered consciousness and hyperthermia, characterising NMS. Alimemazine was stopped and dantrolene and supportive measures, including ventilation under sedation and paralysis with midazolam and vecuronium, were started. As clinical symptoms remained unabated, increasing doses of bromocriptine were administered. Two days after maximal bromocriptine dosage, her clinical condition improved and paralysis and ventilation were stopped. Midazolam and bromocriptine could be gradually decreased and suspended during the following months. A few days after bromocriptine cessation NMS recurred and was complicated by a fatal cardiorespiratory arrest. *Conclusion*: caution must be exercised when prescribing alimemazine, especially to children with basal ganglia damage and in the case of inexplicable fever and restlessness, neuroleptic malignant syndrome should be considered. Long-term therapy with bromocriptine combined with dantrolene and midazolam may be a successful medical treatment.

Keywords Alimemazine · Neuroleptic malignant syndrome · Phenothiazines

Abbreviation NMS neuroleptic malignant syndrome

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Introduction

In addition to their antipsychotic action, phenothiazines also have sedative, anti-emetic and anti-allergic characteristics for which they are regularly prescribed. A rare but very serious side-effect of this medication is neuroleptic malignant syndrome (NMS). Although all phenothiazines can trigger this syndrome [5], chlorpromazine and promethazine are specifically cited and mainly in adults [1, 2]. This case illustrates that alimemazine, frequently used in children, can also trigger NMS.

Case report

This case involves a 4-year-old girl with multiple handicaps and epilepsy as result of perinatal asphyxia. CT scan of the cerebrum showed basal ganglia necrosis and cortico-subcortical gliosis. Because of feeding problems, the patient had a gastrostomy catheter.

From 4 months prior to admission, the patient exhibited restlessness, increasing epileptic symptoms and regularly subfebrile temperature. Medical treatment consisted of 14 mg baclofen and 440 mg valproic acid, both thrice daily. To treat the restlessness, alimemazine was started at 10 mg, once daily. All medication was administered by gastrostomy catheter. One and a half months before transfer to our hospital, she was admitted elsewhere because of inconsolable crying. Subsequently, she had temperature increases up to 40°C, without microbiological focus and increased muscle tone, decreased consciousness and increasing restlessness. Therefore, 10 days before her transfer, the alimemazine dose was doubled to 20 mg, and almost daily 1–2 extra doses of 10 mg were given. Despite addition of i.v. midazolam, at 0.1 mg/kgper h, agitation and motor restlessness increased for which she was transferred to our tertiary centre.

We saw a sick, restless, and multiple handicapped girl with decreased consciousness, a weight of 17 kg and a temperature of 38°C. In addition to the spastic tetraplegia, there was also rigidity. Twelve hours later there was serious agitation and motor restlessness, a further decrease in consciousness, paleness, tachycardia and fever rising to 41.3°C. She perspired heavily, demonstrated severe extension spasticity with tetany and a tense tremor of the extremities. An EEG ruled out status epilepticus, no focus for infection was found and metabolic work-up did not reveal any abnormalities. Blood levels of valproic acid and alimemazine proved to be within the therapeutic range. Laboratory studies showed leucocytosis (23.8×10^9/l), an increased GGT (44 U/l), SGOT (101 U/l), LDH

(927 U/L), CK (3043 U/L) and myoglobinuria. Given the clinical picture of extra-pyramidal motor disturbances, autonomic disorder, lowered consciousness and hyperthermia, in combination with the above-mentioned laboratory abnormalities, NMS was diagnosed.

Alimemazine and baclofen were stopped and dantrolene 40 mg i.v. four times per day (9.4 mg/kg per day) was started. The hyperthermia was treated with external cooling, paracetamol and generous i.v. fluids. Because of subsequent risk of exhaustion, the patient was intubated and ventilated under sedation (midazolam 0.3 mg/kg per h, i.v.) and paralysis (vecuronium 0.1 mg/kg per h, i.v.). The symptoms of rhabdomyolysis subsequently decreased over a period of days (decreased CK and cessation of myoglobinuria). As, 3 days after the start of treatment, the clinical symptoms were unabated, 0.5 mg of bromocriptine was administered, thrice daily via gastrostomy catheter and over a period of 5 days increased to 3 mg, thrice daily (0.53 mg/kg). Eight days after the start and 2 days after maximal bromocriptine dosage, the patient's clinical condition clearly improved, evidenced by more stable and less hypertensive blood pressure, and temperature decrease (to 38°C). After suspending paralysis and ventilation, symptoms returned to a minimal but acceptable degree. Four days later, a start was made on gradually decreasing the midazolam.

Seven weeks after admission, the patient was discharged in a satisfactory condition, comparable with the period preceding this episode. At that time, apart from the valproic acid, she was being given 20 mg of dantrolene four times (continued for her spasticity), 2.5 mg of bromocriptine, three times, and 1.5 mg of midazolam, five times per day. It was possible to suspend the administration of midazolam after 4 and that of bromocriptine after 8 weeks. A few days after bromocriptine cessation she became acutely ill, with high fever and dyspnoea and was readmitted to our hospital. She appeared sick, with a respiratory frequency of 60/min, cardiac frequency of 210/min, blood pressure of 170/30 mm Hg, saturation 100% with 2 l of oxygen via nasal cannula, and temperature of 40°C. She was pale-grey, had cold extremities, poor capillary refill and demonstrated extension hypertonicity. Because of probable recurring NMS, possibly in combination with pneumonia or sepsis, bromocriptine was restarted, dantrolene continued and broad-spectrum i.v. antibiotics were administered. Radiological studies showed pneumonia, but cultures of sputum and blood showed no trace of pathogen. CK was 300 U/l (slightly elevated). The patient expired shortly after admission due to cardiorespiratory arrest. Permission for an autopsy was withheld.

Discussion

NMS is rare in children; in adults treated with neuroleptics a frequency of 0.5% to 1.4% is cited [10]. Throughout the world, Silva et al. [11] found 77 described paediatric cases from 1966 to 1998 in Medline and from 1994 to 1998 in Psychinfo, with an average age of 15 years. Only a few patients under 6 years were mentioned.

NMS involves a clinical diagnosis for which so far no universal criteria have been established [11]. Diagnosis can, however, be made with great certainty when four phenomena are observed: extra-pyramidal motor dysfunction with rigidity, autonomic dysfunction, decreased consciousness and hyperthermia. While biochemical parameters as leucocytosis, elevated transaminases and CK support the diagnosis, they are not obligatory. An elevated CK is considered by some to be a major criterion [8] and occurs in about 97% of patients [1]. It goes without saying that other causes (particularly infectious or neurological) must first be ruled out.

From 1.5 months before NMS was diagnosed, our patient increasingly demonstrated all the above-mentioned diagnostic clinical symptoms plus supporting abnormal biochemical parameters. An infectious aetiology was absent. The period before that could be viewed as a preliminary phase to NMS, supported by the occurrence of restlessness despite increasing doses of alimemazine, subfebrile temperatures and increased epileptic symptoms [4,12]. Velamoor et al.[12] found that in 70.5% of the described clinical pictures, the sequence of symptoms was as follows: (1) mental changes, (2) rigidity, (3) hyperthermia, and (4) autonomic dysfunction, consistent with our patient.

The name of the clinical picture implies prior treatment with antipsychotics, formerly known as neuroleptics. However, stopping dopaminergic medication can also be the trigger [1]. Although the exact pathogenesis is not clear [1, 3], it is generally assumed that the primary factor is blockade of dopamine receptors in the striatum and the hypothalamus [1]. Our patient was treated with alimemazine. This is a classical antipsychotic with the associated risk of numerous extrapyramidal side-effects but nevertheless regularly prescribed as a sedative for children. NMS as a side-effect has not previously been described prior to 2002.

Cerebral damage at the site of the basal ganglia may have been a predisposing factor in our patient. Given the dysbalance of dopaminergic input, a blockade of dopaminergic receptors (for example by alimemazine) could more rapidly lead to NMS. The literature mentions an association with striatonigral degeneration [6, 7]. In general it is assumed that NMS occurs within 2 weeks of starting treatment with anti-psychotics or increasing the dose, but periods up to 30 days have also been mentioned [1, 11]. In the our case, alimemazine was given in increased dose frequency during the first few months. This may have contributed to the gradual development of the syndrome, followed by an acceleration after doubling the dose and extra administrations 2 weeks before diagnosis was established. Although the high dose (up to 2 mg/kg) can have had a predisposing action, NMS has also been described in association with low doses of neuroleptics [1]. At the final admission, the patient again displayed all the associated clinical symptoms, probably triggered by bromocriptine cessation, hence recurring NMS. At the time CK was only slightly elevated, which neither strongly supports the diagnosis nor rules it out. In addition, because of the acute development of the syndrome and prior administration of dantrolene, it may not have been possible for the CK to have risen further (highest values reached after 1–2 days). The pneumonia and heart failure that occurred are consistent with the most common complications of NMS [1].

No complete agreement has yet been reached with respect to treatment. Although measures such as discontinuing neuroleptics and administration of antipyretics and sufficient fluids are self-evident, opinions are divided when it comes to medication. As no single medication seems appropriate, combinations are sometimes preferred [1]. The most commonly cited and effective medications are the peripheral muscle relaxant dantrolene and the

dopamine-agonists amantadine and bromocriptine [1, 9]. Benzodiazepines are used less often but can have a beneficial effect [1, 9]. This is possibly generated by indirect dopaminergic effects, mediated by GABA-ergic feedback loops in the nigrostriatal and mesolimbic centres [1, 9]. We found that a combination of dantrolene, bromocriptine and midazolam produced beneficial therapeutic effects. Weight-related dosages of bromocriptine, that cannot be administered parenterally, are not mentioned in the literature. In this case a dose of 0.53 mg/kg, divided into three doses, proved effective. Regarding the duration of medical treatment, administration of bromocriptine for 10 days is assumed to be effective [9]. In our patient, however, a much longer (3–4 months) administration and a very gradual decrease of both bromocriptine and midazolam was necessary. The fact that recurrent NMS followed bromocriptine cessation suggests that the patient was bromocriptine dependent at that time.

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