Malignant neuroleptic syndrome

Malignant neuroleptic syndrome (hereinafter referred to as **MNS**) is relatively rare, but serious and life threatening complications arising from the treatment of neuroleptics. It manifests as parkinsonism and hyperthermia.

History and Epidemiology

It was first described in 1960 by Delay et al. in connection with the clinical testing of **haloperidol**, however over time it has been described casuistically with neuroleptics of all types. More often, it is linked to the use of high-potency neuroleptics and depot preparations. However, the development of MNS has also been described after **antiemetics** and **sedatives** with weak neuroleptic properties (metoclopramide, promethazine). According to various authors, the incidence varies between 0.07-3.2% and the reported mortality also varies between 10 and 25%. A strong predictor of mortality is renal failure, with the manifestation of which the risk of death increases up to 50%.

Pathogenesis

The pathogenesis of MNS is still not fully understood and there are several different theories. The two most likely are **neuroleptic-induced alteration of central neuroregulatory mechanisms** and abnormal response of predisposed skeletal muscle. Other theories trying to shed light on the pathogenesis of MNS include the possibility of a **direct toxic effect** of neuroleptics on normal skeletal muscle.

- **The Theory of central blockade of dopamine receptors** is supported by an experiment in which by instilling dopamine into the hypothalamus it is possible to lower the temperature of the body's core. When D receptors are blocked, a higher temperature can occur. This theory is also supported by the good response of the MNS to substances that increase the activity of the dopaminergic system in the CNS (bromocriptine, amantadine) and through the blockade of the dopaminergic system it is also possible to explain other components of the syndrome (rigidity). Also, the development of symptoms corresponding to MNS has been repeatedly described in patients who were suddenly stopped from treatment for Parkinson's disease, and some of them were not even treated with neuroleptics.
- **The theory promoting the effect of a primary skeletal muscle defect** (similar to that of malignant hyperthermia) is supported by experiments performed in vitro on muscle fibers biopsied from patients who developed MNS; further, the similarity of MNS with malignant hyperthermia (hyperthermia, rigidity, elevation of creatine kinase, similar mortality) and, last but not least, a good response to dantrolene therapy, present in both conditions. Unfortunately, the contractility tests performed so far cannot be summarized in the form of a meta-analysis due to the different methodology used in the individual studies.

Risk Factors

Risk factors include **young age**, **male gender**, presence of **affective symptoms**, and **organic CNS involvement**. Patients with extrapyramidal disorders are particularly at risk. In addition, increased caution should be observed in patients who are physically exhausted, dehydrated, in patients with an unrecognized concurrent infectious disease or with hormonal imbalance. Caution is also needed with alcoholics in the early phase of abstinence.

Diagnostics

A uniform set of diagnostic criteria does not exist, however, a typical **tetralogy** of symptoms is repeatedly described including **extrapyramidal symptoms** (so-called lead-pipe rigidity), **alterations of consciousness**, **increased temperature** to hyperpyrexia, **autonomic instability**. Other typical (laboratory) findings are **leukocytosis** without shift to the left and multiply increased values of **creatine kinase**. All this in relation to antipsychotic therapy in the previous 7 days (or 2-4 weeks for depot preparations). Some authors also report an increase in myoglobin in urine and serum, which would correspond to ongoing rhabdomyolysis. Progression to full expression usually takes 24-72 hours.

Differential diagnosis

In terms of differential diagnosis, it is necessary to think about the possibility of **CNS infection** (lumbar puncture), **metabolic or endocrine disorders** (thyrotoxicosis), **autoimmune disease** (SLE). A similar set of symptoms can also be observed in malignant hyperthermia (reaction to succinylcholine), serotonin syndrome, pheochromocytoma or lethal catatonia. Among rarer causes, tetanus and strychnine poisoning should also be considered.

Therapy

The success of therapy depends mainly on early recognition and rapid withdrawal of neuroleptics from medication. Furthermore, **general symptomatic** treatment such as hydration, good nutrition and fever reduction is recommended. A significant effect on reducing fever is described with electroconvulsive therapy (ECT). However, to reduce the risk of hyperkalemia in patients with developed rhabdomyolysis, it is recommended to use some of the **non-depolarizing myorelaxants** (atracurium, vecuronium) instead of the popular succinylcholine. It is also advisable to use **dantrolene** to manage hyperpyrexia. Among other substances, there are good results with **dopamine agonists** (bromocriptine, amantadine, but also levodopa). Although they do not seem to have a direct effect on temperature or rigidity, some authors describe a temporary relief of difficulties after administration of **benzodiazepines** (diazepam, lorazepam); in any case, they can be used for general calming of agitated patients during MNS treatment. It is recommended to provide the patient with a low dose of heparin right at the beginning to reduce the risk of venous thrombosis. However, the syndrome often resolves spontaneously after discontinuation of antipsychotics.

The risk of recurrence of MNS in case of continued use of antipsychotics reaches 30%. To reduce it, it is necessary to focus on limiting risk factors such as dehydration, and it is also advisable to consider alternative forms of therapy (to antipsychotics). E.g. treatment of bipolar disorder is also possible with lithium or ECT. A lower risk of developing MNS is also reported when using atypical antipsychotics, compared to typical ones. The renewed administration of neuroleptics is advisable to start with lower doses, titrate the resulting dose slowly, and if possible, in the first 14 days after the end of MNS, the patient should not receive neuroleptics at all. According to prof. Hrdlička should not already be treated with neuroleptics other than clozapine.

Links

Related Articles

- Neuroleptics

References

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