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RISPERIDONE-INDUCED NEUROLEPTIC MALIGNANT SYNDROME : A CASE REPORT

G. VENKATASUBRAMANIAN, B.H. YOGANANDA & B.N. GANGADHAR

ABSTRACT

A young male schizophrenic presented with neuroleptic malignant syndrome (NMS). Risperidone was the probable precipitating agent. Rigidity and elevated CPK levels poorly responded to bromocriptine. but showed good response to dantrolene. The role of specific treatment and the differential response of the symptom clusters are discussed.

Key words : NMS, risperidone, dantrolene and bromocriptine

Neuroleptic malignant syndrome (NMS) is a rare, but potentially fatal and idiosyncratic reaction to neuroleptics (Delay & Deniker, 1968; Henderson & Wooten,1981; Morris et al.,1980). This syndrome consists of extra-pyramidal signs of rigidity and tremor; autonomic signs of hyperthermia, labile blood pressure, tachycardia, tachypnea, fever and diaphoresis; cognitive disturbances like confusion and altered sensorium; biochemical disturbances in the form of elevated creatine phosphokinase (CPK) (Delay & Deniker,1968; Henderson & Wooten, 1981). NMS has occurred mostly in patients receiving typical antipsychotics (Shalev et al.,1989). There are reports of NMS following atypical neuroleptics like risperidone, clozapine (Hasan & Buckley,1998) and olanzapine (Johnson & Bruxner,1998). We report a case of NMS involving risperidone and the usefulness of specific treatment, particularly bromocriptine and dantrolene.

CASE REPORT

Mr.A, a 22 year old male, is a case of paranoid schizophrenia (DSM-IV) of four year duration with positive as well as negative symptoms, and without any treatment. He was started on treatment with injection fluphenazine decanoate 25 mg i.m. fortnightly (suspected poor compliance) and chlorpromazine 400 mg PO/day. In view of prominent negative symptoms, severe EPS and no perceptible improvement with above drugs for four weeks, risperidone was started and was increased to 4 mg/day gradually. Six days after starting risperidone, the patient developed mild confusion and agitation. He left the hospital against medical advice. Three days later, the patient presented to the hospital with features of cognitive disturbances in the form of confusion and altered sensorium; autonomic instability in the form of profuse diaphoresis, tachycardia (100-120 beats per min.), tachypnea (22-26 respirations per min.), labile blood pressure (systolic varying between 130-150 mm Hg and diastolic varying between 90-100 mm Hg), fever (100 °F); neuromuscular disturbances in the form of generalized, extreme rigidity and tremors. He was without any documented infection. The CPK level at the time of admission was 4438U/L. His WBC count was 14,600 per cu. mm. The results of cranial CT scan, chest X-ray, lumbar CSF analysis, metabolic profile and urine analysis were within normal limits.

A diagnosis of NMS (Levenson,1985) was made. The antipsychotics were stopped and

supportive care was instituted. There was improvement in his autonomic instability and CPK level decreased to 1908 U/L. Other clinical features continued to worsen. The patient was started on bromocriptine on the fourth day. After 36 hours of treatment with bromocriptine (7.5 mg/day, PO) there was improvement in cognitive disturbances. But, the rigidity remained the same and the CPK level rose upto 2957 U/L. So the patients was started on dantrolene which was gradually increased upto 200 mg/day at the rate of 50 mg every two days. Bromocriptine was increased upto 20 mg/day at the rate of 5 mg every two days. Neuromuscular disturbances disappeared gradually over a period of 10 days and CPK level came down to 216 U/L. Dantrolene was tapered and stop over two days because of abnormal liver function tests (elevation of serum glutamate oxaloacetate transferase, serum glutamate pyruvate transferase, and alkaline phosphatase levels) after starting the drug. With the discontinuation of dantrolene, the rigidity re-emerged and the CPK level rose from 216U/L to 918 U/L (Figure). As literature evidence favours dosage of bromocriptine upto 60 mg/day (Caroff & Mann, 1993), an attempt was made to increase bromocriptine. It had to be aborted due to re-emergence of symptoms like irritability and sleep disturbances. The rigidity continued to worsen and the CPK level was increasing. Dantrolene was restarted after five days and all signs improved and CPK level dropped down to 213 U/L in next two days. Repetition of liver function tests after restarting dantrolene did not show any abnormality. After ten days of patient being in a stable condition, bromocriptine and dantrolene were tapered and stopped. The patient recovered fully without any residual deficit.

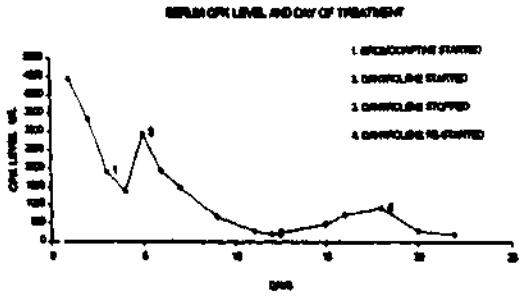

Fig. Effect of Dantrolene on serum CPK. Although, there was an instantial initial drop in serum CPK, it rose again while the patient was only on bromocriptine and began to fall only after treatment with Dantrolene. Stopping this drug led to CPK elevation which again responded to Dantrolene treatment

DISCUSSION

Our patient was on typical neuroleptics for nearly one month before starting treatment with risperidone. The manifestations on NMS in this case had been noticed within a week after starting risperidone. It has been observed that majority of patients (66%) who develop NMS do so within the first week of treatment with the offending agent (DSM-IV). It is likely, therefore, in this case risperidone was responsible in either causing or precipitating NMS.

We suggest that the clinical features of NMS can be grouped into four clusters based on their response to treatment viz., autonomic disturbances, cognitive disturbances, neuromuscular disturbances and biochemical disturbances. Autonomic disturbances decreased with the stoppage of antipsychotics and supportive care. Cognitive disturbances were improved by treatment with bromocriptine. Neuromuscular disturbances and biochemical perturbations required dantrolene (Figure). Dantrolene is a skeletal muscle relaxant, which acts mostly through peripheral mechanism in improving the rigidity. Two possible mechanisms have been implicated for rigidity in NMS. First one, which postulates the central dopaminergic blockade, may not fully explain the rigidity in NMS, as bromocriptine, which is a dopamine agonist, was ineffective. Second mechanism is the peripheral one, which involves an impairment of the sarcoplasmic reticulum re-uptake of calcium in a genetically abnormal muscle as is proven in malignant hyperthermia (Bismuth et al., 1984). Our case report supports the latter mechanism, since the rigidity continued to worsen when the patient was on bromocriptine alone and it promptly improved after the reinstitution of dantrolene.

In summary, risperidone can cause or precipitate NMS. There may be different clusters of symptoms, which may not respond to conservative treatment alone. Specific treatment like dantrolene may be necessary particularly for neuromuscular disturbances.

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G. VENKATASUBRAMANIAN, MBBS,Junior Resident, B.H. YOGANANDA, MD, Senior Resident & B.N. GANGADHAR, MD, Additional Professor, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore-560029.*

Correspondence