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Neuroleptic Malignant Syndrome: A Focus on Risk, Recognition and Antipsychotic Re-Challenge

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Introduction

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal adverse drug reaction, most commonly to antipsychotic medications, characterised by muscle rigidity, hyperthermia, delirium and autonomic instability. Although NMS is relatively uncommon, with an estimated incidence of around 0.9% of those on antipsychotic medications over an 18 month period [1], the estimated mortality has been reported between 5.6% to 12% [2,3] and therefore prompt treatment is essential.

Risk Factors

Identifying clinical risk factors for NMS enables clinicians to recognise those individuals most likely to develop the syndrome. Several authors have previously studied the risk factors for developing NMS [4]. Tse et al. have grouped these risk factors into four categories; pharmacological, environmental factors, demographic details and genetic background [3]. Although the precise incidence rates varied slightly by treatment setting and country there is limited evidence to suggest that these are significant risk factors in the development of NMS [3].

The pharmacological risk most commonly relates to treatment with antipsychotic medication or following withdrawal of dopaminergic agents [1,5]. Several aspects of antipsychotic treatments have been found to contribute to the risk of developing NMS, including high dosages, dose increases and the early phases of antipsychotic treatment. Parenteral administration, combining antipsychotic agents and polypharmacy have also been associated with an increased risk, but there is no conclusive evidence that using either typical or atypical antipsychotics contributes greater risk [3,6].

Environmental factors relate to dehydration and high core temperatures as well as physical restraint. Advancing age appears to be a contributing factor and the average age of patients with NMS has been found to be 46.9 years [4]. There also seems to be a potential genetic link as patients with previous episodes are more likely to experience a recurrence, as are those with a family history of NMS [7]. Similarly, patients with a previous history or family history of catatonic syndrome also have an increased risk of NMS and there is evidence of a potential overlap between these syndromes [8]. Indeed, three subtypes of NMS have been proposed based on catatonic features; those in whom catatonic symptoms precede onset of NMS, concurrent NMS and catatonic symptoms and those with NMS without catatonia [9]. While the sample size was too small determine definitive differences in clinical course, risk factors or demographics between subtypes, further case reports have suggested that NMS with catatonia may be a benzodiazepine responsive subtype [10], while other studies have demonstrated symptom overlap between non-catatonic NMS and serotonin syndrome [11]. A systematic review of case reports also demonstrated that NMS associated with atypical antipsychotics may present with atypical features such as fewer extrapyramidal symptoms, although the presence of catatonia was not examined [12].

Recognition and Diagnostic Criteria

A lack of definitive diagnostic criteria for NMS may severely hamper recognition of a condition with serious consequences, where early treatment can be lifesaving [13]. There are numerous diagnostic criteria that have been suggested for NMS with small but important variations between them [14-20]. Differences have centred on exact measurements of temperature, heart rate, blood pressure and creatine kinase required for NMS diagnosis and the relative importance of each criterion. Gurrera et al. [19] have attempted to address this issue by developing. An International Expert Consensus (IEC) on NMS criteria As well as defining the critical values and specific criteria necessary for a diagnosis of NMS, these criteria include a weighted scale, giving varying importance to each criterion out of a total 100 points [21]. More recently, IEC criteria have been validated against previous records of NMS diagnoses, in order to generate potential cut-offs scores which could be used to diagnose NMS [21]. This study found that a cut-off score of 74 gave sensitivity 69.6% and specificity 90.7% compared to modified Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. While the absence of an objective biological marker to confirm NMS makes it impossible to compare criteria for diagnostic accuracy, the principle behind the IEC criteria appears to be a promising tool both for NMS and potentially other psychiatric conditions.

Management and Antipsychotic Re-Challenge

The management of NMS remains primarily supportive and includes the immediate discontinuation of the antipsychotic agent, monitoring of vital signs, fluid resuscitation, correction of electrolyte imbalances, cooling and removal of restraint [1,22,23]. Additionally, there is well documented evidence for the effectiveness of pharmacological agents such as benzodiazepines, dantrolene, bromocriptine and amantadine in the management of NMS. Electro-Convulsive Therapy (ECT) can also be used in severe cases that have not responded to medication, with good evidence of recovery from NMS and some control of psychiatric symptoms [24]. However, the reintroduction of antipsychotics in a patient who has experienced NMS is particularly challenging as guidelines are lacking and evidence is reliant upon case reports or series in which longer term outcomes are seldom reported [1]. Ideally the reintroduction of antipsychotics should be avoided, but in patients with chronic psychotic illness this is unlikely to be a feasible strategy and

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careful consideration of the risks and benefits of antipsychotics needs to be considered in each individual case.

The recurrence rates of NMS in those restarted on antipsychotics vary from 13-37% [25,26], although the majority of patients can continue on antipsychotics safely. A number of principles are apparent from the best literature evidence, which suggest that a "*washout*" period between the resolution of NMS symptoms and the reintroduction of an antipsychotic agent may be important, with advice ranging from 5-14 days [25,27,28]. Most studies switched to a different antipsychotic for re-challenge and the use of an atypical agent with low D_2 receptor affinity such as Quetiapine [29], Olanzapine [30,31] or Clozapine [32,33] is recommended [1,34], while successful re-challenge with Aripiprazole, a partial agonist at D_2 receptors, has also been reported [13,35]. However, notable case series did not find recurrence was related to the medication used [25,27]. Additionally, there are reports of successful re-challenge with the same antipsychotic medication, usually Clozapine, where patients with treatment resistant illness were unable to be successfully treated with alternative antipsychotics [32,36,37]. A low starting dose of antipsychotic medication with careful titration and monitoring while informing patients and carers about the key features of NMS are other important aspects of antipsychotic reintroduction strategy [1,34], while avoiding the use of depot or parenteral antipsychotics [22].

Conclusion

In conclusion, NMS is an uncommon but life threatening condition which requires early recognition and immediate medical management. Diagnosis remains challenging due to multiple criteria, but attempts are being made refine and standardise these. It is inevitable that due to the patient group receiving antipsychotics, many will require reintroduction of medication, although this should always be considered a risk-benefit decision on an individual basis, involving patients and carers in the discussion wherever possible. Current recommendations from the literature are to allow 14 days after resolution of symptoms before reintroducing antipsychotics, to restart with an atypical antipsychotic with low D_2 receptor affinity at a low dose with careful monitoring for signs of recurrence.

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