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When Psychosis Meets Ptosis: A General Practice and Multidisciplinary Approach to Recognising Mitochondrial Neurogastrointestinal Encephalopathy

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Abstract **Review Article**

When mental health issues coexist with seemingly unconnected physical conditions, the diagnosis process can become extremely complicated, necessitating a multidisciplinary approach and heightened clinical awareness. Mitochondrial neurogastrointestinal encephalopathy is an uncommon but significant example of a condition where mild neurological and gastrointestinal symptoms may appear and possibly conceal underlying metabolic abnormalities. With an emphasis on psychiatric, neurological and gastrointestinal symptoms that could complicate diagnosis, this featured review investigates how general practitioners (GPs) and multidisciplinary teams (MDTs) can identify atypical presentations of MNGIE. We emphasize the importance of general care in negotiating the intricacies of these uncommon multisystemic illnesses, as well as clinical hints and diagnostic techniques.

Keywords: Autosomal recessive disorder, Psychiatric symptoms, Neurogastrointestinal, Thymidine phosphorylase gene.

INTRODUCTION

Mitochondrial Neurogastrointestinal Encephalopathy is a rare, autosomal recessive disorder caused by mutations in the thymidine phosphorylase gene, leading to mitochondrial alterations and impaired oxidative phosphorylation (Campos *et al.,* 2019; Manski *et al.,* 2022).

MNGIE is usually encountered in the first or second decades of life, with an average onset age of 18.5 years, though cases have been reported as early as five months and as late as the fifth decade (Bax, 2019).

MNGIE is a progressive, degenerative disease characterized by gastrointestinal dysmotility, peripheral neuropathy, progressive external ophthalmoplegia, cachexia, and diffuse leukoencephalopathy (Tawk *et al.,* 2020).

In MNGIE, psychiatric symptoms can frequently mask the clinical picture, making diagnosis particularly challenging. In mitochondrial dysfunction, oxidative stress and monoaminergic dysregulation there may be disturbances in the serotonin, dopamine, and norepinephrine pathways. Patients with MNGIE have been found to have problems with neurotransmitter synthesis, reuptake, and receptor binding (Rawani *et al.,* (2024). This can result in mood swings, cognitive impairments, and behavioural changes that may be mistakenly thought to be exclusively psychiatric in nature (Baglioni *et al.,* 2024).

There is growing evidence that the development and course of several neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis, are substantially influenced by mitochondrial dysfunction (Clemente-Suárez *et al.,* 2023).

Many patients first exhibit symptoms that are frequently confused with basic psychiatric disorders, such as depression, anxiety, or even psychotic episodes. These symptoms could manifest long before more obvious symptoms of MNGIE, such as muscle weakness or gastrointestinal symptoms. As a result, patients are sometimes misdiagnosed and given psychotropic drugs for mental health conditions that may worsen

mitochondrial dysfunction in addition to being ineffective. White matter changes may be seen in brain scans, but if MNGIE is not recognized, these results could be incorrectly linked to other neurological or mental illnesses. This overlap makes it easy to miss the underlying mitochondrial cause.

For clinicians, it is important to think beyond psychiatric labels when symptoms don't fully add up—especially in younger patients whose mood or cognitive symptoms are paired with unexplained digestive issues or a suggestive family history. Catching MNGIE early can make a significant difference, offering the chance for more appropriate care and a better quality of life.

Because psychiatric symptoms manifest years before other recognized signs, clinicians should consider MNGIE in patients presenting with psychiatric issues, particularly when accompanied by unexplained gastrointestinal distress or neurological abnormalities.

Gastrointestinal symptoms include chronic diarrhoea, abdominal pain, early satiety, nausea, vomiting, and dysphagia, often leading to misdiagnosis as malabsorption syndrome, inflammatory bowel disease, or anorexia nervosa (Habibzadeh *et al.,* 2020).

Neurological symptoms initially may be subtle and can be missed easily. These may include peripheral neuropathy, progressive external ophthalmoplegia, and diffuse leukoencephalopathy, which contributes to diagnostic delays (Tawk *et al.,* 2020).

Understanding the connection between gut health, mental health, and mitochondrial function is crucial (Alshial *et al.,* 2023; Delanote *et al.,* 2024).

CLINICAL CASE SCENARIO (HYPOTHETICAL CASE)

In addition to persistent nausea, vomiting, and growing muscle weakness, a 24-year-old woman appears to her general practitioner (GP) with psychotic symptoms, such as delusions and auditory hallucinations. Since her early twenties, she has experienced frequent stomach pain and distension, which was first diagnosed as irritable bowel syndrome. In the last 12 months, she has developed drooping eyelids (ptosis) and difficulty swallowing. Neurological examination reveals ptosis and peripheral neuropathy. The initial diagnostic workup focuses on psychiatric causes for psychosis and common gastrointestinal disorders, and MNGIE is not initially considered. Further questioning reveals a family history of unexplained neurological symptoms in a sibling, prompting the GP to broaden the differential diagnosis. This includes rare metabolic disorders such as MNGIE.

RECOGNISING RED FLAGS

Psychiatric symptoms that may be new or worsening, if present with gastrointestinal and neurological symptoms or either of these, should raise the suspicion of MNGIE.

When patients present with above symptoms, it is essential to probe more and be vigilant. It may seem like a straightforward mental health case at first glance, but this could be the beginning of complex underlying problem like mitochondrial disorders. These conditions can be commonly missed or misdiagnosed.

- **Unexplained gastrointestinal symptoms**: When accompanied by malnourishment and weight loss, chronic nausea, vomiting, diarrhoea, stomach pain, and early satiety might raise concerns of underlying gastrointestinal dysmotility disorders, including MNGIE.
- **Symptoms of the nervous system**: Neurological signs such as peripheral neuropathy or dysautonomia, if present with behavioural changes often indicate systemic disorders affecting the nervous system and should not be attributed solely to psychiatric causes (Bax B.E.,2020). Consideration of mitochondrial disorders should be prompted by progressive external ophthalmoplegia, ptosis, muscle weakness, and cognitive deterioration.
- **Family history**: Suspicions for inherited metabolic disorders should be raised if there is a family history of unexplained neurological or gastrointestinal illnesses.
- **Resistance to conventional treatment**: When gastrointestinal or mental health disorders don't improve with routine treatments, the diagnosis should be reevaluated.
- **Neuroimaging Abnormalities and Psychiatric symptoms:** Young adults with psychiatric symptoms and Diffuse white matter changes on MRI may indicate leukoencephalopathy, often seen in mitochondrial encephalopathies like MNGIE (Hirano *et al.,* 2021).

INVESTIGATIONS AND DIAGNOSTIC APPROACH

When MNGIE is suspected, clinicians are encouraged to use a combination of biochemical, genetic, and radiological investigations. This integrated approach helps confirm the diagnosis while also ruling out other potential causes (Tawk *et al.,* 2020).

Biochemical testing plays a key role in the diagnostic workup of MNGIE. This typically involves measuring thymidine and deoxyuridine levels in plasma and urine, which are markedly elevated in affected individuals due to a deficiency in thymidine phosphorylase (Pacitti *et al.,* 2018). These findings can provide strong biochemical evidence to support further genetic and clinical investigations.

A muscle biopsy can provide helpful clues when mitochondrial dysfunction is suspected. By examining the tissue, clinicians can assess how well the mitochondrial respiratory chain is working and look for ragged red fibres in gomoritrichome strain (Hamsa *et al.,* 2021) distinctive signs often seen in mitochondrial disorders. These findings can strengthen the diagnosis, especially when other tests are unclear.

Gastrointestinal symptoms are common in MNGIE and often need further investigation. Endoscopy, colonoscopy, and small bowel biopsies can help assess how well the digestive system is working. These tests are useful for detecting signs of dysmotility and ruling out other possible causes (Hamsa *et al.,* 2021). They also help guide the next steps in management.

Radiological tests are important in the assessment of neurological symptoms. An MRI of the brain can help detect leukoencephalopathy, a common feature in MNGIE. This finding can support the diagnosis and help distinguish it from other neurological conditions (Farahvash *et al.,* 2021).

Genetic testing is essential for confirming a diagnosis of MNGIE. This involves checking for mutations in the *TYMP* gene, which are responsible for the condition (Slama *et al.,* 2005). Identifying these mutations provides a definitive diagnosis and helps guide family counselling.

MANAGEMENT PRINCIPLES

MNGIE management is primarily supportive, focusing on alleviating symptoms, providing nutritional assistance, and slowing disease progression. While there is no definitive cure, these measures aim to improve quality of life and reduce complications associated with the condition.

MULTIDISCIPLINARY APPROACH.

Managing MNGIE effectively requires a team effort. General practitioners, gastroenterologists, neurologists, psychiatrists, geneticists, and dietitians all play important roles. Working together helps provide comprehensive care and improves outcomes for patients.

Nutritional support

Malnutrition is a common concern in MNGIE. Dietary treatments such as enteral and parenteral nutrition are often essential to address this issue. These approaches help maintain strength and support overall health (Hirano, 2016).

Gastrointestinal symptom management

Managing gastrointestinal symptoms is a key part of MNGIE care. Medications like prokinetics and antiemetics can help improve gastric emptying and reduce nausea. Pain relief may also be needed to improve comfort and quality of life (Corazza *et al.,* 2018).

Psychiatric management

Psychotropic medications may help with mood and psychosis but must be used cautiously. For patients and their families to manage the difficulties of having a chronic and progressive illness, psychological support and counselling are crucial. CBT and support groups can help with coping and quality of life.

Neurological management

Neurological management involves a complete rehabilitation program. This would include occupational and physical therapy. Aim is to ameliorate motor impairments, promote mobility, and foster independence in activities of daily living. This would overall enhance patient functionality and well-being. For neuropathic pain, gabapentin or pregabalin may be considered.

Specific therapies:

- Haematopoietic stem cell transplantation has shown promise in restoring enzyme activity (Dasu *et al.,* 2022).
- Enzyme replacement and gene therapy are emerging options (Filosto *et al.,* 2018).

Genetic counselling

Genetic counselling should be offered to patients and their families as part of comprehensive care. This provides an opportunity to discuss the risk of recurrence in future generations and to explore available reproductive options in an informed and supportive setting.

Future directions

The development of more potent treatments for MNGIE may be possible with research into novel therapeutic targets like gene therapy, enzyme replacement therapy, and substrate reduction therapy (Tawk *et al.,* 2020). Further research on genetic disorders that cause mitochondrial abnormalities is necessary to expand treatment options in managing MNGIE.

Key points

- MNGIE is an uncommon genetic condition that can present with psychiatric, gastrointestinal and neurological symptoms.
- Consider MNGIE in patients with psychiatric issues and unexplained GI or neurological features.
- TYMP gene testing, plasma thymidine and deoxyuridine levels and distinctive leukoencephalopathy on MRI confirms diagnosis (Filosto *et al.,* 2011).
- To evaluate GI dysmotility, endoscopy and colonoscopy are used (Spagnoli *et al.,* 2018).
- Management is mostly supportive, emphasising interdisciplinary care.
- For prompt intervention and better results, early detection of MNGIE is essential.

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