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Psychiatric Care for a Person with MELAS Syndrome: A Case Report

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Abstract

A patient with MELAS *[mitochondrial-encephalomyopathy, lactic-acidosis & stroke-like-episodes]* syndrome developed psychological and behavioural disturbances. Psychiatric multidisciplinary interventions such as psychopharmacology, psychiatric-nursing, behavioural-therapy and occupational-therapy were involved. The goal of empowering the parents to manage challenging behaviours remained unmet. Understanding the psychological concept of "naturing over time' and importance of timely caregiver-intervention may achieve better outcomes in this group of patients.

Keywords. *MELAS, Behaviour Therapy, Sensory Deficit, Psychiatric Nursing, Occupational Therapy, Multidisciplinary Team, Case Report*

Introduction

The psychiatric and behavioural manifestations of mitochondrial diseases are varied. **[[1], [2]]** Studies have shown that psychiatric illnesses are common in patients with mitochondrial diseases. **[[3], [4], [5]]** However, the treatment of psychiatric conditions in this population has not been well established. Many psychotropics have detrimental effects on the mitochondria and hence may not be deemed suitable to prescribe or use for these patients. Psychotherapeutic approaches and behavioural therapies could be more suitable; however, these modalities could also be limited by several disease factors such as cognitive impairment, physical impediment and the unpredictable occurrences of behaviour states. **[2]**

This case-report described a patient with diagnosed MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) syndrome who at a later stage of his illness, had developed psychological and behavioural disturbances. MELAS syndrome is caused by mutations in the mitochondrial DNA, most commonly MT-TL1. The narrative followed through the psychiatric evaluation, the inpatient therapy and the many challenges faced in the treatment of this patient. Both of the patient's parents had provided explicit consent for the information to be published in the hope that the medical community would be better equipped to manage such issues.

Case History

The patient was a 26-year-old Chinese male named JWH [a] and he was not diagnosed with MELAS syndrome at first. He had initially presented to the general paediatric unit at fourteen years of age for prolonged fever with an altered mental status. **[[6]]** An electroencephalogram (or EEG) showed ongoing seizures. He was then diagnosed to suffer from an episode of viral encephalitis and treated appropriately. In the subsequent years, he had multiple re-admissions for recurrent partial seizures, or cortical seizures affecting his visual tract, and even left-sided hemiparesis. A further workup was ordered, beginning with Magnetic Resonance Imaging (MRI) and then Spectroscopy (MRS) which revealed a duplex *"lactate peak"* alongside an elevated serum lactate of 3.6mg/dL. JWH's diagnosis was then revised to MELAS syndrome. His treatment commenced with intravenous Arginine with good clinical response. Over the course of the following twelve years after the diagnosis of MELAS, JWH's effort tolerance gradually deteriorated due to the development of hypertrophic cardiomyopathy, a sensori-neural hearing loss, cortical blindness (secondary to bilateral occipital infarcts) with macular sparing, as well as progressive muscular weakness.

[a] JWH is a fictitious acronym and does not compromise anonymity.

Timeline and Diagnostic Assessment

An incident had occurred when he turned twenty-six years old. He had been aggressive towards another player at a mini-golf course after a misunderstanding ensued between them. Angrily, he had raised a golf club against her and caused injury. Security personnel separated them, and JWH was conveyed to a psychiatric hospital for evaluation. He had become more irritable with frequent mood swings. He was placed on psychiatric follow-up for four months and Fluoxetine 20 milligrams daily was prescribed to curb the episodes. The SSRI [b] antidepressant caused him daytime sedation. Although a switch to Sertraline was suggested, JWH and his parents were not keen to continue on medications. He was subsequently lost to follow up with that local psychiatric hospital and had stopped psychiatric medication.

The following year after that index psychiatric assessment, JWH's parents sought help from his paediatric neurologist for escalating aggression. He was found to have cognitive decline with worsening of neuropsychiatric symptoms over the fortnight, along with poorer intake and early satiety. The observed symptoms included talking and muttering to himself about having "*a third eye*", seeing objects wobbling around (established not to be visual hallucinations but a result of how he verbalized or perceived his deteriorating vision), speaking out of context or irrelevantly (established to be a result of worsening hearing impairment and not primary thought disorder), as well as disturbed sleep. He had stayed up in the night and talked to himself. He became increasingly irritable and displayed violence towards his parents. JWH grew resentful when he could not get his needs met on time. At the time of assessment, his anger outbursts required no apparent reasons or triggers. JWH's mother described how he would chase after her to land a punch on her hence she had to hide behind locked bedroom. Despite so, she still worried if JWH would fall and injure himself because of his frail physique.

JWH was referred to Psychiatry during that visit for worsening behavioural changes and escalating aggression towards his parents. He was admitted to the paediatric high-dependency unit (HDU) from the clinic while waiting for the psychiatric consultation-liaison (CL) team. JWH's challenging behaviours started manifesting such as pacing up and down the HDU demanding to leave, repeatedly saying how the environment was not to his liking, *"…that it was so cold (I) could freeze to death and that the ceiling was full of germs…*" and adding that no one could fool him. He required chemical restraint and was transferred to the psychiatric ward in view of his inability to restrain his emotions and hyperactivity.

[b] SSRI, Selective Serotonin Reuptake Inhibitor

The impression from the CL team was that of **emotional and behavioural disturbances secondary to neurocognitive decline on a background of MELAS with significant medical complications**.

Subsequent re-assessments showed that JWH was prone to irritability and temper tantrums. He would frequently get annoyed when he construed that circumstances and situations were not to his liking. His sensory impairments also worsened these behaviours. This led to him displaying verbal and physical aggression towards staff and other patients in the psychiatric ward. He adamantly denied feeling depressed, yet often lamented about his poor health and unpleasant experiences in the hospital. He had voiced passive suicidal ideation but had never demonstrated any self-harm attempts. He did not report auditory hallucinations or any paranoid ideation. JWH's parents observed decline in his general function. He had worked for a short while as a cleaner in a food centre but would get into frequent arguments with customers and colleagues. Mental-state-examination revealed a small-built Chinese male who appeared older than his biological age, with features of under-nourishment and muscle atrophy. He had hearing and visual impairment and would respond with a loud and threatening voice. He was verbally aggressive and confrontational. Objective test scores were attempted without any yield. He could not perform in the Montreal Cognitive Assessment due to his visual impairment. Despite this, his cognitive symptoms appeared to correlate with the severity of the cerebral atrophy shown in his MRI.

Various Therapeutic Interventions

Pharmacological Treatment

Many classes of psychotropic medications are found in-vitro to negatively affect mitochondrial function, and these include SSRIs, SNRIs, [c] MAOIs, [d] antipsychotics, sodium-valproate although these agents have not been studied in a clinical setting. Therefore, prescribing psychotropics for symptom management becomes a challenge for patients with mitochondrial disorders exhibiting psychiatric symptoms. JWH had previously used Fluoxetine and Sertraline (SSRIs), with minimal improvement in mood-state and impulse-control. These medications made him excessively sedated during the day and exacerbated his irritability. The psychiatric team decided to trial Mirtazapine (NaSSA) [e] after examining the literature in order to stabilise his mood state and aimed to reduce his irritability. The additional effects of increasing his appetite and improving his sleep were beneficial. At the same time, a trial of Pregabalin (GABA) [f] was initiated for anxiolysis and preferred over prolonged reliance on benzodiazepine to contain

[c] Serotonin-Noradrenaline Reuptake Inhibitor
[d] Mono-Amine Oxidase Inhibitor
[e] Noradrenaline & Specific Serotonergic Antidepressant
[f] Gamma-Amino-Butyric Acid

the aggression. To reduce breakthrough agitation, very-low doses of Clonazepam were judiciously administered. The medications were well-tolerated in the ward's structured milieu albeit for unpredictable moments of daytime somnolence.

Non-Pharmacological Treatment

A. Attenuation Of Sensory Deficits:

One significant contributor to JWH's outbursts was his frequently misunderstood auditory cues due to his bilateral sensori-neural hearing loss. The team encouraged use of his hearing aids. The other sensory deficit was his cortical blindness with macular sparing. JWH would be startled and became hypervigilant when he was approached by staff or patients from his side. The team made efforts to educate everyone including his family members to directly approach him from his front, where his vision was relatively intact.

B. Psychological And Behavioural Therapy:

In the ward, it became apparent that there were psychological nuances to JWH's presentation. The anger and agitation were manifestations of his inner-psyche, made worse when he found himself unable to vocalise or to be understood effectively. JWH suffered from an inferiority complex. Culturally, being the only male child in a Chinese family meant that he had been expected to continue the family lineage. He recurrently lamented about what his older sisters had achieved in life such as marrying their partners of their choice and having the freedom to leave home. These milestones had made JWH feel like "*the sick child*" – someone left behind, unwanted and unloved. JWH's parents had also seen him getting jealous and edgy during weddings of their family-friends' children. JWH behaved similarly if he saw his peers romantically partnered. In JWH's feeble attempts to conceal his muscle weakness (due to myopathy from MELAS), he would flex his biceps and even perform squats in front of ward staff to show that he was never a weakling. This display of "*manhood*" sometimes escalated to physical aggression and became more pronounced when he faced persons taller in stature and bigger in physique than him. He would hurl insults loudly like "*small doctor!*" in his first attempt to belittle and frighten staff "*into submission*". JWH often grieved over the decline of his physical health and his frequent prolonged hospitalizations due to MELAS. Another contributory factor to this may be the "*way of communication*" JWH was used to from his father's parenting style by using physical punishments. The father had been taught not to use this anymore because JWH could assimilate that as the only way to interact with people.

The ward psychologist recommended a method building on Acceptance & Commitment Therapy to build his acceptance towards his illness. Delivery of psychotherapeutic material was limited by JWH's

communication deficits, cognitive impairment and his challenging behaviours with emotional upheaval. The therapist might be curtly shouted at to leave him. On days when JWH was in better form, he could engage in meaningful conversations with the psychologist albeit in a slowed and truncated manner. His grief toward his illness made it exceptionally difficult to move towards acceptance.

JWH's parents might have contributed partly to this phenomenon as they pursued a "*cure with medication*'. Although they accepted the illness' inevitability, the parents still maintained that medication might still cure or reverse his behavioural problems. They also expected absolute recovery with cessation of aggression. The Advanced Practice Nurse (APN) attempted to moderate their expectations and provide psychoeducation on numerous episodes that psychotropics would have limited effect without parental and behavioural management. JWH's parents had also been taught how he had been "*natured over time*". The paediatric neurology and adult medicine teams managing JWH understood the same concept. "*Natured over time*" described JWH's current "*attitude*" towards his parents. JWH would be cordial with ward patients and the nurses. The instance JWH's mother appeared in the ward, JWH would march to his bedside cabinet, dragged out his bag of old clothes and flung it to his mother's feet shouting, "*What took you so long? Take this and wash!*" At other times, JWH had raised fists at the mother for not attending to his requests immediately. The staff had to intervene and invite JWH's mother to leave. At the mother's departure, JWH then returned to his "*own routine*" in the ward such as sitting by his bedside table and quietly eating.

Individual cognitive psychotherapy was difficult as JWH could not remember and retain well due to poor vision and cognitive decline, and he found it difficult to retain meaningful new information or perspectives presented to him. JWH had continued to ruminate over unpleasant experiences such as Intensive Care Unit admissions and painful medical procedures. The team decided to focus on behavioural modifications and worked with his parents on the implementation of behavioural tactics and management, and successful transfer of these skillset back home. Therefore the implementation of a simple reward-disincentivizing system was used. During episodes of aggression, the attending nurse would firmly, in an audible volume and tone, instruct him to sit on the allocated chair besides his bed and his family members would be asked to leave the space momentarily. Over time, it was hoped that JWH would learn to appreciate his family's visitations more. The staff made it a point to treat JWH as an 'equal' rather than in a condescending manner. JWH also liked to be independent in his b-ADL [g] as he resented being guarded and monitored.

[g] Basic Activities Of Daily Living

C. Psychiatric Nursing:

Evidence for nursing-care specific for persons with MELAS was sparse. The nurses adopted methods including assisting JWH to adapt to new environments, recognising the need for caregiver support, and knowing JWH as a person and seeking to understand what he lived through, what made him agitated and what would make him calmer or friendlier. What helped tailor the team's nursing interventions to suit JWH's nursing needs was the assessment of his behaviour using the ABC (Antecedent, Behaviour and Consequences) template. Charting JWH's behavioural patterns helped immensely with medication administration and behaviour modification. By intervening to prevent the antecedent, communicating (at JWH's level of cognitive understanding) on the potential consequences, and redirecting him to other tasks or activities, the problem behaviour can be reduced. **[**[7]**]**

Nursing care revolved around his strong desire for independence. JWH would get upset if anyone attending to him "*doubted*" his independence. Examples of nursing care-plans individualized for JWH included encouraging his mobility (working with his unsteady gait) around his bedside and placing basic necessities near and around him, and not to offer assistance even if he was seen trying to scoop and constantly spilling his food.

D. Mental Health Occupational Therapy

The mental-health occupational-therapist (MHOT) had used various activities and games to engage JWH. These included simple arithmetic manipulations, visual and sensory puzzles, playing-cards to name a few. His hearing and visual impairment hindered his ability to engage thereby causing him frustration. He was averse to socialisation and was not suited to join groups though eventually some of the younger patients could approach him. Cognitively complex activities were unsuitable for him. He enjoyed interactive games on a tablet (with a larger screen) that involved moving large, brightly-coloured shapes. This was to build his confidence and ability to enjoy games.

Two artworks of JWH were shown with his parents' permission to illustrate his attempt at drawing with pen-and-paper **(Figure 1)** and colouring with an iPad **(Figure 2)**. In Figure 1, despite poor vision he was trying to draw a picture of himself, showing him wearing his favourite yellow jacket (the yellow bits). In Figure 2, the therapist had used an iPad to guide him in picking colours to fill a picture, of which he dedicated this to his mother.

Follow-up and Outcomes

JWH's temper eased with both pharmacological and non-pharmacological interventions. Following interventions, he appeared calmer and appeared uplifted. A lower sedating dose of Mirtazapine was given in the morning instead of the night and when he was observed to be angrier and talking with a louder voice. Medication therapy set the stage for de-escalation and distraction.

The goal towards the later part of his hospitalization was to empower his parents to care for him and manage his challenging behaviours. JWH began to initiate interest in MHOT activities and built rapport with the nursing team who could discern JWH's likes and dislikes. The parents was only confident marginally. At the last family conference, the family decided for institutionalisation. The mother being the main carer had lost confidence and become fearful of reliving the trauma of being battered by JWH. The mother was further upset by the observation that JWH continued to treat outsiders (staff and other patients) better than his own parents. The parents continued to feel powerless despite concurred improvement and trials of parent-child activity and home-leave.

Unfortunately, during JWH's prolonged hospitalization in the psychiatric ward, he developed a stroke-like episode and lactic acidosis. He was started on intravenous Arginine and transferred to the HDU. He developed status epilepticus requiring multiple antiepileptics but eventually succumbed to his neurodegenerative illness. The family was hoping the experience that the team and JWH had together, could be put together to help future sufferers with similar situations go through treatment successfully.

Discussions

The care for JWH would not be possible without a multidisciplinary team approach and multi-prong interventions from various team. There is importance in timing the medication and adjusting its frequency to match the behavioural occurrences to pre-empt and prevent the episodes. In JWH's case, Mirtazapine timing was oddly used in the early morning but that had aided him greatly.

The team also realised that better outcomes may be more achievable with earlier referral for psychiatric and behavioural intervention in this group of patients. Patients with rare genetic diseases with young onset and protracted course may carry inherent risks of emotional and relationship problems, possible future violent behaviour, substance misuse and comorbid mental illnesses like depression. These might be mitigated by addressing childhood behaviour problems early by adopting strategies targeted at removing ineffective parenting skills and helping parents build confidence and skillsets to handle difficult situations **[8]** , before the problem behaviour became too fixed and harder to treat. As caregivers live with

the problem behaviour longer, they can get traumatized or become too enmeshed or used to the problem behaviour, making it more difficult for them to change and manage their child's problem behaviour by the time they seek professional help.

Declaration

Ethics Approval and Consent to Participate:
Not applicable.

Consent for Publication:
Written informed consent to publish this information was obtained from study participants.
Informed consent for publication had been obtained patient's parents via institutional consent form.
The manuscript contains no identifier or personal or clinical details that will compromise anonymity.

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