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# Neuropsychiatric Sequalae of Fahr's Disease: An Atypical Presentation of Psychosis

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## ABSTRACT

**Background: Fahr's Syndrome is a rare neurodegenerative disorder characterised by bilateral, symmetrical calcifications of the basal ganglia, thalami, hippocampus, cerebral cortex, cerebellum and centrum semiovale. The neurological symptoms include motor symptoms, gait and sensory abnormalities; and seizures. Neuropsychiatric manifestations vary from delirium, depression, psychosis and mania with neurocognitive symptoms follow subcortical dysfunction. Case Report: Ms EC is a 42-year-old female who presented as an index patient following a month of aggressive behaviour, mania and psychosis. She displayed subcortical neurocognitive symptoms for an unknown duration. Her past medical history revealed adult-onset epilepsy four years prior to this presentation with her last reported seizure in 2018. Results: Calcium, magnesium and phosphate were subtherapeutic. EEG displayed abnormal ictal activities and a long bone x-ray indicating hyperostosis. CT brain imaging revealed linear ependymal calcification along occipital horns of the lateral ventricles, bilateral basal ganglia and thalamic and cerebellar calcification with confirmed T2 flair MRI images confirming bilateral, asymmetrical white matter hyperintensities involving periventricular tracts. Diagnostic Formulation: 1. Fahr's syndrome due to hypoparathyroidism, 2. Mood and psychotic disorder due to Fahr's Syndrome, 3. Major neurocognitive disorder due to possible Fahr's Syndrome with psychotic symptoms, 4. Epilepsy, 5. Subclinical hypothyroidism, 6. Bilateral eye cataracts. Parenteral calcium, magnesium, thiamine, folate and vitamin D oral supplements were prescribed. Olanzapine was titrated to 10mg, following a failed trial of risperidone. Lamotrigine was prescribed to augment the therapeutic sodium valproate. Upon discharge, her pharmacological treatment consisted of: 1) Lamotrigine 75mg per os (po) bi-daily (bd), 2) Epilim CR 300mg po bd, 3) Vitamin D supplementation, 4) Eltroxin 75ug po daily, 5) Olanzapine 15mg po nocte, 6) Titralac 2 tabs po ter die sumendum (tds), 7) Folate 5 mg po daily, 8) Thiamine 100mg po tds. A referral to ophthalmology was made regarding the cataract's diagnosis. Conclusion: Radiological and biochemistry investigations should be motivated for in resource limited settings when assessing atypical psychosis. This case report highlighted neurobehavioral and neurocognitive symptoms may develop and persist in a patient with Fahr's syndrome.**

**Keywords:** Fahr's disease, neuropsychiatry, neurocognitive, neurobehavioural sequalae, calcium- Ca, liver function tests- LFT, magnesium Mg, parathyroid hormone- PTH, phosphate- Phos, computer topography- CT, magnetic resonance imaging- MRI, fluid attenuated inversion recovery- FLAIR.

## INTRODUCTION AND BACKGROUND

Fahr's Syndrome, first described by Karl Theodor Fahr in 1930 (1), is a rare neurodegenerative disorder that results in neurological, neurocognitive and neurobehavioural symptoms. The condition is primarily characterised by bilateral, symmetrical calcifications of the basal ganglia. Further neuroanatomical areas affected include the thalami, hippocampus, cerebral cortex, cerebellum and centrum semiovale (2). While the pathogenesis is not clearly understood, endocrinopathies related to calcium metabolism, parathyroid illness, infections, toxins and genetic links have been implicated (3-7).

Pathological processes resulting in a striato-pallido-dentate distribution are most associated with disorders of calcium metabolism and hypoparathyroidism, (8) with a prevalence ranging from 25-74% (13). The most common underlying cause of Fahr's syndrome resulting from hypoparathyroidism is idiopathic/familial hypoparathyroidism. Postsurgical hypoparathyroidism was the second most common cause, with the mean time of diagnosis described up to approximately 30 years post thyroidectomy (13). The impaired modulations of calcium coupled with low serum calcium/phosphate results in basal ganglia calcification in hypoparathyroidism. The perfusion, metabolism and periventricular location of the globus pallidus makes it particularly vulnerable to the imbalances (5).

The neurological symptoms range from hypokinetic (parkinsonism, dystonia) to hyperkinetic motor symptoms (chorea, tremor), gait abnormalities (ataxia), sensory symptoms (paraesthesia) and seizures (9). The neurobehavioural manifestations range between delirium, depression, psychosis and mania (10, 11). Neurocognitive symptoms follow subcortical dysfunction with case reports describing dysexecutive symptoms, impaired complex attention with anterograde amnesia, impaired working memory and decreased processing speed (12). Further deficits described in a case more than 12 months post diagnosis included deficits in divergent thinking, mental flexibility with a sparing of the higher order functions such as language and perceptuomotor function (12).

The expression of such symptoms and the severity thereof have been proportionally linked to an increased deposition of calcium in the basal ganglia and surrounding brain matter (14). This may be explained by the role of the basal ganglia in the cortico-subcortical networks, particularly the connections of the prefrontal and frontal areas, which are responsible for various motor, associative and limbic functions (15).

Criteria aimed at assisting in diagnosing Fahr's disease have evolved over the years. Proposed diagnostic criteria (16) were summarised based on various reviews of the literature (adapted from Moskowitz et al. and Ellie et al.) (17) (18) entailing aetiologies, pathophysiology and radiological findings:

- Radiological evidence of bilateral calcification of the basal ganglia.
- Neurological and neuropsychiatric manifestations with onset usually in the fourth or fifth decade, although this dysfunction may also present earlier.



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- Absence of biochemical abnormalities and somatic symptoms indicative of a mitochondrial or metabolic disease or other systemic disorder.
- Absence of other causes accountable by infections, toxic, or trauma related.
- Family history consistent with autosomal dominant inheritance when considering Fahr's Disease.

The clinical presentation coupled with supportive radiological findings and biochemical changes (indicative of hypoparathyroidism) are important in diagnosing Fahr's Syndrome due to endocrinology pathologies. Laboratory investigations to investigate secondary causes of brain calcifications include:

1. Haematology and Metabolic panels
2. Serum calcium (Ca), magnesium (Mg) and phosphate (Phos), liver function tests (LFT)
3. Calcitonin, vitamin D, parathyroid hormone (PTH)
4. Blood and urine heavy metal levels
5. Cerebrospinal fluid analysis for bacteria, virus, and parasites
6. Ellsworth Howard test (following 200 U PTH injection, 10-to-20-fold increase in urinary cAMP levels)

Imaging studies reveal similar findings in both Fahr disease and Fahr's syndrome (aetiology from secondary causes). Computer topography (CT) brain imaging may reveal calcifications in various areas including the lentiform nucleus, dentate nucleus, thalamus, cerebellum and brain stem. Although magnetic resonance imaging (MRI) is preferred in defining anatomical areas, it is considered less sensitive for detecting calcium deposits compared to CT imaging. This may be explained by heterogenous signal intensities which can result in misinterpretations (19). Nuclear functional imaging may reveal impaired metabolism and perfusion in the basal ganglia. The management of Fahr's syndrome is predominantly focused on symptomatic management, relieving symptoms and addressing any reversible causative aetiologies with the use of a multidisciplinary team in the correct setting. Psychotropics should be considered to target psychiatric manifestations while considering the propensity for these medications to lower seizure threshold e.g., lithium in symptomatic individuals. Anti-epileptics should be initiated in patients with seizures and co-morbid mania however with consideration of these medication's risk of affecting movement and gait. Symptoms of Fahr's syndrome as a result of parathyroid disorder must be managed with the correction of phosphate and calcium levels (16).

In the presence of limited controlled data, the treating team should be cognisant of side effects, drug-drug interactions and the propensity to worsen symptoms of affected individuals, particularly with the use of psychotropics.

## CASE REPORT

Ms EC is a 42-year-old, unemployed female, with a grade 8 education. She was admitted to Helen Joseph Hospital (secondary level care facility) in Johannesburg, on the 21 January 2022. She presented as an index mental health care user following a month of aggressive behaviour, mania and psychosis. Psychotic symptoms consisted of auditory and visual hallucinations, grandiose and somatic delusions. On further enquiry from collateral sources, Ms EC displayed neurocognitive symptoms of subcortical dysfunction for an unknown duration, prior to the onset of neurobehavioural symptoms. These symptoms included deficits in working memory

(difficulty holding instructions), executive functions (required assistance in making decisions regarding instrumental activities of daily living like shopping or going to a hospital appointment) and impaired attention (struggles with sustaining, shifting, selecting or dividing attention with increased distractibility).

Her past medical history revealed an admission for adult-onset epilepsy, four years prior to this index presentation. She had bilateral tonic-clonic seizures complicated by status epilepticus. This required intensive care, prolonged intubation and tracheostomy. Neuroimaging from this admission was not available. Her last reported seizure was in 2018 and antiepileptic agents were stopped by the outpatient clinic team at an unknown time. She has cataracts which impacted on her visual acuity, with severity steadily progressing over approximately 3 years. Due to her presentation, an index workup was completed which included radiological and serological investigations as depicted in table 1. A diagnosis of delirium was made due to noted derangements in biochemistry resulting in an admission to the medical ward for investigation and management.

**Table 1: Investigations conducted during her stay in the medical ward consisted of the following:**

| Investigations | 20/01/22 | 24/01/22 | 26/01/22 | 03/02/22 | 14/02/22 | 03/03/22 | 05/04/22 |
|---|---|---|---|---|---|---|---|
| Sodium mmol/L | 139 | 135 | | | 137 | | |
| Potassium mmol/L | 3.7 | 4.6 | | | 3.9 | | |
| Chloride mmol/L | 99 | 103 | | | 101 | | |
| Urea mmol/L | 3.2 | 3.5 | | | 4.8 | | |
| Creatinine mmol/L | 79 | 75 | | | 93 | | |
| Glomerular filtration rate | 80 | 85 | | | 65 | | |
| Total protein g/L | 80 | | | | | | |
| Albumin g/L | 45 | | | | | | |
| Total bilirubin umol/L | 47 | | | | | | |
| Conjugated bilirubin umol/L | 14 | | | | | | |
| Alanine transaminase U/L | 20 | | | | | | |
| Aspartate transaminase U/L | 20 | | | | | | |
| Alkaline phosphatase U/L | 122 | | | | | | |
| Gamma-glutamyl transferase U/L | 23 | | | | | | |
| C-Reactive protein mg/L | <4 | | | | | | |
| White cell count $x10^9$ /L | 6.34 | | | | | | |
| Haemoglobin g/dL | 12.6 | | | | | | |
| Platelet count $x10^9$/L | 288 | | | | | | |
| Human immunodeficiency virus serology | negative | | | | | | |
| Cerebrospinal fluid analysis | NAD | | | | | | |



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|---|---|---|---|---|---|---|---|
| Calcium mmol/L | **1.52** | **1.74** | 2.18 | **1.95** | **2.12** | 2.11 | **1.96** |
| Magnesium mmol/L | **0.61** | 0.72 | 0.82 | 0.86 | 0.83 | 0.7 | 0.8 |
| Phosphate mmol/L | **1.59** | **1.68** | **2.56** | **3.07** | 1.38 | 1.14 | **2.14** |
| Parathyroid hormone | **1.1** | | | | | | |
| Vitamin B12 | 392 | | | | | | |
| Sodium valproate level umol/L | **44** | | 732 | 712 | | | |
| HBA1C% | | | | | | 5.5 | |
| Total Cholesterol mmol/L | | | | | | 2.86 | |
| Thyroid stimulating hormone mIU/L | **8.29** | | | | | **7.3** | **8.08** |
| Thyroxine (free T4) pmol/L | 17.4 | | | | | **10.9** | 12.6 |
| Treponema pallidum antibodies | negative | | | | | | |
| Hepatitis screen | negative | | | | | | |

The electroencephalogram (EEG) conducted on the 24/01/2022, prior to pharmacological intervention, displayed ictal activity. An x-ray of long bones indicated hyperostosis with no evidence of fractures. CT images of the brain obtained on admission revealed the linear ependymal calcification along occipital horns of the lateral ventricles (image 1), bilateral basal ganglia and thalamic calcification (image 2), bilateral cerebellar calcification (image 3). MRI of the brain (T2 FLAIR) further confirmed bilateral, asymmetrical white matter hyperintensities involving periventricular tracts (image 4):

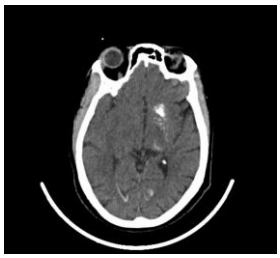
**Image 1**

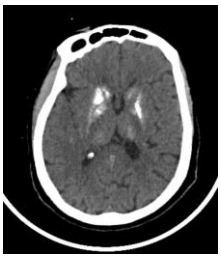
**Image 2**

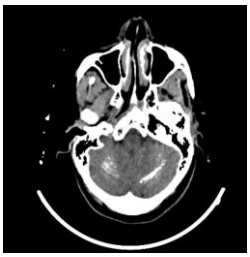
**Image 3**

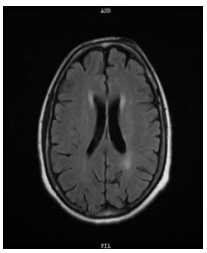
**Image 4**

The neuropsychiatry team was consulted for the co-management of ongoing disorganised behaviour. Her mental state examination at the first consultation revealed an alert, calm and cooperative, fairly groomed, middle aged woman of small stature. She was soft spoken and engaged well in the interview. She displayed no abnormal movements. She appeared distractible with relevant thought form and delusional content. Her mood was euthymic and reactive. She displayed impaired insight and poor judgement.

Her physical examination consisted of the following:

- Her vitals were: Blood pressure = 118/68mmHg; pulse = 81 beats/min; respiratory rate = 20 breaths/min, and a random glucose = 5.8mmol.

She appeared generally well looking with no pallor or peripheral oedema. She had poor dentition with missing and loose teeth and a tracheostomy scar was noted.

The respiratory and cardiovascular examination revealed no abnormalities. The neurological examination revealed decreased visual acuity due to the cataracts. No further focal neurological deficits were detected. Parenteral calcium and magnesium replacement to correct hypocalcaemia and hypomagnesaemia were administered by the medical team which was converted to oral supplementation once calcium and magnesium were corrected. Additionally, she was prescribed thiamine, folate and vitamin D oral supplements.

She was started on risperidone 2mg nocte for psychotic symptoms, which was titrated by 1mg weekly to 4mg nocte. The emergence of akathisia on risperidone prompted a switch to olanzapine 7.5mg nocte. Olanzapine was titrated to 15mg nocte and clinical response and tolerability was observed. During the admission, the patient had breakthrough seizures. Lamotrigine was prescribed in addition to the sodium valproate which was already at a therapeutic level. On discharge she was managed on the following pharmacological treatment:

1) Lamotrigine 75mg po bd
2) Epilim CR 300mg po bd
3) Vitamin D supplementation
4) Eltroxin 75ug po daily
5) Olanzapine 15mg po nocte
6) Titralac 2 tabs po tds
7) Folate 5 mg po daily
8) Thiamine 100mg po tds

During the course of her admission, she received input from the multi-disciplinary team with the aim of improving functionality. An outpatient program was designed for continued care and rehabilitation. A referral was made to the ophthalmology department to address the impact of the cataracts on her visual acuity. The patient was readmitted nine months after her index admission, with acute delirium and elevated blood pressure. The precipitant was identified as non-adherence to treatment. Investigations ordered are illustrated in table 2. During the course of the admission, neuropsychiatry was reconsulted as she displayed persecutory delusions towards her partner. The correction of metabolic abnormalities, the reinitiation and titration of treatment, contributed to remission of symptoms. Extensive psychoeducation was conducted with the patient and family, with emphasis on the importance of the diagnosis and reiteration of adherence to the treatment plan.

**Table 2: Investigations during second admission.**

| **Investigations** | **22/10/22** | **25/10/22** | **31/10/22** | **09/11/22** | **12/12/22** |
|---|---|---|---|---|---|
| Sodium mmol/L | 122 | 137 | 140 | | 139 |
| Potassium mmol/L | 2.9 | 3.8 | 4.0 | | 4.5 |
| Chloride mmol/L | 80 | 100 | 96 | | 101 |
| Urea mmol/L | 2.6 | 2.1 | 5.5 | | 4.7 |
| Creatinine mmol/L | 107 | 103 | 90 | | 126 |
| Glomerular filtration rate | 55 | 57 | 68 | | 45 |
| Total protein g/L | 79 | | | | |
| Albumin g/L | 46 | | 43 | | |
| Total bilirubin umol/L | 10 | | 8 | | |
| Conjugated bilirubin umol/L | 3 | | <2 | | |
| Alanine transaminase U/L | 27 | | 16 | | |


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|---|---|---|---|---|---|
| Aspartate transaminase U/L | 27 | | 15 | | |
| Alkaline phosphatase U/L | 81 | | 66 | | |
| Gamma-glutamyl transferase U/L | 23 | | 12 | | |
| C-Reactive protein mg/L | <10 | | | | |
| White cell count $x10^9$ /L | 6.36 | | 5.08 | | 7.02 |
| Haemoglobin g/dL | 13.2 | | 12.1 | | 11.9 |
| Platelet count $x10^9$/L | 390 | | **181** | | 366 |
| Calcium mmol/L | **1.67** | | 2.10 | 2.28 | 2.46 |
| Magnesium mmol/L | 0.76 | | 0.79 | 0.72 | 0.79 |
| Phosphate mmol/L | 1.24 | | **1.48** | **1.68** | **1.68** |
| Parathyroid hormone | **rejected** | | **0.7** | | |
| Vitamin D (total) nmol/L | 66.16 | | | | |
| Thyroid stimulating hormone mIU/L | | | | | 2.95 |
| Thyroxine (free T4) pmol/L | | | | | 18 |

Treatment on discharge, one month after the second admission, remained the same as per the previous regimen.

The patient is still receiving ongoing care and rehabilitation as an outpatient with a diagnostic formulation consisting of the following:

1. Fahr's syndrome due to hypoparathyroidism
2. Generalised tonic-clonic epilepsy
3. Mood disorder due to Fahr's Syndrome
4. Psychotic disorder due to Fahr's Syndrome
5. Major neurocognitive disorder possibly due to Fahr's Syndrome
6. Subclinical hypothyroidism
7. Bilateral eye cataracts

## CONCLUSION AND RECOMMENDATIONS

A standard operating protocol with appropriate radiological and biochemistry investigations should be applied when assessing atypical presentations of psychosis and adult-onset seizures. This case report highlights that neurobehavioural and neurocognitive symptoms may develop and persist in a patient with Fahr's syndrome. The importance of continuity of care, treatment adherence and psychoeducation are highlighted in this case report. These factors contributed to early identification of pathology on relapse and the recommencement of appropriate treatment resulting in a shortened hospital stay. Further research focussing on psychotropics and its relationship to calcium homeostasis, as seen in Fahr's syndrome, is required to assist clinicians in effective treatment prescriptions.

### Ethics Approval and Consent to Participate

Informed, written consent has been obtained from the patient witnessed by next of kin. Anonymity of patient information maintained.

### Consent for Publication

Not applicable to the current study.

## Declarations
None

## Availability of Data and Materials Statement
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

## Competing Interests
The authors declare that they have no competing interests.

## Clinical Trial Number
Not applicable

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Not Applicable to this current study.

## Authors' Contributions
All authors contributed to the literature review, case report write-up and have read and approved the final manuscript.

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