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AN INHERITABLE STROKE DISORDER PRESENTING WITH UNIPOLAR PSYCHOTIC DEPRESSION: CASE REPORT OF A RARE ENTITY

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ABSTRACT Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant rare hereditary angiopathy that causes stroke in young patients. Most frequent clinical presentations include ischemic strokes, recurrent transient ischaemic attacks and migraine with aura. Psychiatric manifestations are conspicuously rare and especially if present as the only presenting manifestation. Here is a case of a female patient in her fifties who was diagnosed with major depressive disorder with psychotic features and was on medication for the same for one and a half years with no improvement in symptoms. She was subsequently admitted due to an increased tendency to self-harm and on day 6 of admission had an episode of seizures, which led us to look for organic causes. After a battery of tests and ruling out various differentials, she underwent an MRI which revealed T2 hyperintense signal in bilateral frontal, temporal, parieto-occipetal, and periventricular white matter. Based on MRI findings, family history of her father passing away due to a stroke at age 68 and poor response to antidepressants, she was suspected to have CADASIL. She underwent genetic testing which confirmed the same. The clinical course and distinct facts of the case are divulged below.

KEYWORDS : CADASIL, psychotic depression, mood disorder, NOTCH3, genetics

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare genetic microangiopathy which is autosomal dominant in nature. It is an inheritable stroke disorder that can have a variable clinical presentation, generally starting in early adulthood. The most common clinical presentations include ischemic strokes, recurrent transient ischaemic attacks and migraine with aura[1]. CADASIL can sometimes present solely with psychiatric manifestations. Mood disorders and depression are the most common psychiatric presentations and tend to occur more frequently in older age groups[2]. Psychiatric symptoms, especially if present as the only presenting manifestation, tend to avert suspicion from an organic cause, as was the case in our patient. We looked for organic causes only after the patient had an episode of seizures. Hence, it is important for clinicians to be acquainted with all aspects of this disease presentation and to suspect CADASIL in patients who have had no improvement with antidepressants, positive family history of stroke and white matter hyperintensities on MRI.

CASE PRESENTATION:

A female patient aged 52 presented with a history of decreased energy levels, sad mood, feeling of worthlessness, a tendency to self-harm and insomnia for one and a half years. Additionally, she is afflicted by the false belief that her husband is suffering from severe health issues due to her incompetence as a wife. She firmly believes that she is incapable as a wife and is unable to take care of her husband and kids. Contrary to her conviction, her husband claims to be in perfect health and has had no issues with his health. He also adds that she has no prior history of such complaints. She has no history of discrete episodes of hypomanic or manic symptoms. She was diagnosed with diabetes mellitus 6 years ago and is on medication for the same. Her family history is mostly insignificant except for her father passing away due to a stroke at the age of 68.

At the initial interview, she displayed a severely depressed mood, loss of interest, feelings of guilt and worthlessness, psychomotor retardation and lack of insight. Both physical examination and laboratory screening were within normal limits and there were no symptoms that warranted neurological assessment. She was hence diagnosed with major depressive disorder with psychotic features and put on sertraline and olanzapine. She demonstrated poor response to medication and had no improvement in symptoms. She was subsequently admitted due to an increased tendency to self-harm. She was constantly monitored in the ward. On day 6 of admission, she had an episode of seizures, which lasted for 2 minutes, generalised tonic-clonic in nature. Associated with frothing from the mouth. There was postictal voiding of urine and loss of consciousness. It was not accompanied by tongue bite or bowel disturbances. The episode was not preceded by a history of fever/head injury/ altered sensorium. The episode of seizures was managed immediately with intravenous diazepam.

Ruling out various differential diagnoses went as follows. Routine blood tests, including total counts, glucose, serum electrolytes, calcium, magnesium, kidney and liver function, were done to rule out electrolyte abnormalities, acid-base disorders, infections, and any underlying liver or renal dysfunction. Urinalysis and toxicology screens were done to rule out drug toxicity or overdose. Lumbar puncture was performed and CSF was analysed to rule out CNS infections and antibody screening to rule out autoimmune encephalitis. An echocardiogram and 24-hour ECG were done to look for cardiogenic causes which may have caused secondary seizures.

Routine blood studies and toxicology screens were normal. HIV and VDRL tests were unremarkable. CSF analysis was normal. Antibody screening for autoimmune encephalitis in cerebrospinal fluid was also negative. An echocardiogram and 24-hour ECG did not reveal anything out of the ordinary. The patient was subsequently taken up for an MRI. MRI revealed T2 hyperintense signal in bilateral frontal, temporal and parietal and periventricular white matter (Figure 1).

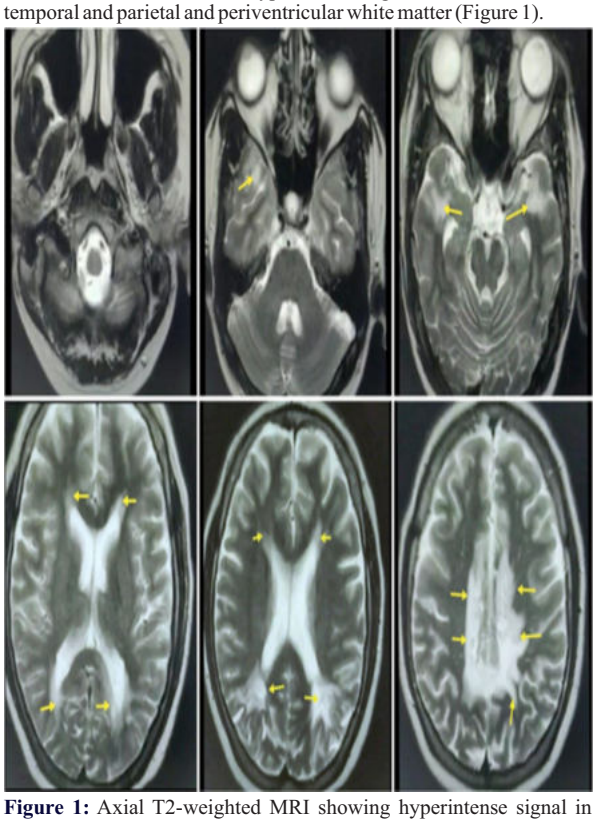

Figure 1: Axial T2-weighted MRI showing hyperintense signal in bilateral frontal, temporal, parieto-occipetal and periventricular white matter.

After ruling out alternate diagnosis as stated above, considering the family history, imaging report and poor response to medication, the patient was suspected to have CADASIL. She underwent genetic analysis which showed a mutation R1006C in exon 19 of the NOTCH3 gene

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There is no specific treatment for CADASIL that can alter the disease course. Management is largely based on symptomatic treatment. The episode of seizures was managed immediately with intravenous diazepam. This patient was put on a prophylactic anti-platelet agent for stroke prevention even though there is no distinct evidence that supports this and continued treatment for major depressive disorder with psychotic features and diabetes mellitus. She was also put on prophylactic levetiracetam to prevent seizures.

The patient is currently 1 year into the diagnosis. She is on regular follow-up and visits the hospital every 2 months. She has not had a recurrence of seizures. She has not had any ischemic attacks as of yet. She is on strict glycemic control and her HbA1c is maintained lower than 7%. She has had little improvement in unipolar psychotic depression.

DISCUSSION:

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a common form of inheritable stroke disorder. It is an autosomal dominant disorder that leads to cerebrovascular manifestations in early adulthood. The mean age at the onset of symptoms is 45 years[3]. In the younger cohort of patients, migraine is a common inaugural symptom, while the older patients more commonly tend to have ischemic manifestations and psychiatric symptoms[3].

It is a monogenic disease, with mutations seen in the NOTCH3 gene located on chromosome 19q13.1[4]. It is an extensive gene which contains 33 exons and encodes for a transmembrane receptor rich in epidermal growth factor repeats expressed in vascular smooth muscle cells and pericytes. NOTCH protein regulates arterial differentiation and maturation of vascular smooth muscle cells[5]. More than 230 pathogenic variants have been reported[6]. These mutations alter the number of cysteine residues in the extracellular domain of NOTCH3 receptors, which accumulate in the small arteries of the skin, retina, brain etc.[7]in the afflicted population, leading to generalised angiopathy. However, vascular complications are notably confined to the brain.

The most common clinical presentations include ischemic strokes, recurrent transient ischaemic attacks and migraine with aura[1]. Symptom profile and disease severity vary widely in the population, sometimes even different affected members of the same family can have varying presentations[1]. Migraine with aura is a common presenting feature in younger patients and in around 20% of the patients occurs as an isolated phenomenon[8]. Guey et al. reported that in patients with migraine with aura, more than 50% of them reported at least one atypical aura such as motor symptoms, confusion or hallucinations[8]. They concluded that in patients suffering from migraine with aura with relevant family history and white matter hyperintensities on imaging, the presence of an atypical aura should raise clinical suspicion of CADASIL.

Cognitive deficits are also commonly prevalent in this disease. Deficits are mostly seen in processing speed (assessed by trail-making test), executive functions, verbal fluency, and attentional deficit. Memory, reasoning and visuospatial functions are relatively well preserved, particularly in the early stages[9]. Other less common manifestations of the disease include seizures, encephalopathy, and cerebral haemorrhage[1][3][10].

The clinical course in adults eventually progresses to ischemic attacks. They tend to be recurrent and can lead to significant cognitive and motor decline and these patients have a higher risk of developing vascular dementia. Most of the ischemic episodes either manifest with classic lacunar features like pure motor/pure sensory strokes, dysarthria-clumsy hand syndrome or as brainstem syndromes[1][3][11].

The significance of CADASIL is understated in psychiatry. Psychiatric symptoms, especially if present as the only presenting manifestation, tend to avert suspicion from an organic cause, as was the case in our patient. It is essential for a clinician to be aware of all aspects of this disease as a whole and even though it is primarily a neurological disease, many patients do not show obvious neurological abnormalities. Mood disorders and depression are the most common psychiatric presentations[2]. They tend to occur more frequently in older age groups. Adjustment disorders are also a frequent entity[1].

Our patient had major depressive disorder with psychotic features. In order to diagnose this, patients must have symptoms of major depression with hallucinations and/or delusions. The psychoses (delusions or hallucinations) in such patients are consistent with depressive themes like guilt, nihilism or death[12][13]. The clinician must be particularly alert while assessing such psychotic symptoms as the patients tend to cloak them due to fear of judgement and hence can be easily misdiagnosed[14]. The symptoms of worthlessness, guilt and suicidal ideation are more intense in these patients in comparison to unipolar nonpsychotic depression[15]. A retrospective analysis of all medically serious suicide attempts made by patients with unipolar major depression, recurrent, with psychotic features undertaken showed that patients with delusions of sinfulness, guilt, deserved punishment, or persecution are more likely to make medically serious suicide attempts than patients with delusions of bodily disease, damage, and malfunction[16].

Depression in vascular conditions like CADASIL is believed to be due to disruption in prefrontal circuits by white matter hyperintensities (WMH). WHMs are the earliest MRI findings in CADASIL and are believed to be present in virtually all patients with CADASIL above the age of 35. A study published by Park et al says that for every 1 mL of WMH volume, the risk of depressive disorder increases by 3%[17] . Hence, the greater the volume of white matter hyperintensities, the greater the risk of developing depressive disorders. Other MRI findings include cerebral microbleeds and lacunar infarcts[17].

CONCLUSIONS:

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebrovascular disease which can have wide-ranging clinical manifestations as a result of which it might be challenging for clinicians to pinpoint the diagnosis. This patient had major depressive disorder with psychotic features that responded poorly to medications and underlying causes were looked into only after the patient had an episode of seizures. Therefore, in patients with consistent deterioration of psychiatric symptoms despite adequate medication and no apparent causes for worsening, in the context of a family history of ischemic attacks and relevant imaging findings, vascular causes such as CADASIL must be given due consideration as a possible differential diagnosis.

REFERENCES:

(1) Dichgans, M., Mayer, M., Uttner, I., Brüning, R., Müller-Höcker, J., Rungger, G., Ebke, M., Klockgether, T., & Gasser, T. (1998). The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Annals of neurology*, *44*(5), 731–739. https://doi.org/10.1002/ana.410440506

(2) Valenti, R., Poggesi, A., Pescini, F., Inzitari, D., & Pantoni, L. (2008). Psychiatric disturbances in CADASIL: a brief review. *Acta neurologica Scandinavica*, *118*(5), 291–295. https://doi.org/10.1111/j.1600-0404.2008.01015.x

(3) Desmond, D. W., Moroney, J. T., Lynch, T., Chan, S., Chin, S. S., & Mohr, J. P. (1999). The natural history of CADASIL: a pooled analysis of previously published cases. *Stroke*, *30*(6), 1230–1233. https://doi.org/10.1161/01.str.30.6.1230

(4) Larsson, C., Lardelli, M., White, I., & Lendahl, U. (1994). The human NOTCH1, 2, and 3 genes are located at chromosome positions 9q34, 1p13-p11, and 19p13.2-p13.1 in regions of neoplasia-associated translocation. *Genomics*, *24*(2), 253–258. https://doi.org/10.1006/geno.1994.1613

(5) Domenga, V., Fardoux, P., Lacombe, P., Monet, M., Maciazek, J., Krebs, L. T., Klonjkowski, B., Berrou, E., Mericskay, M., Li, Z., Tournier-Lasserve, E., Gridley, T., & Joutel, A. (2004). Notch3 is required for arterial identity and maturation of vascular smooth muscle cells. *Genes & development*, *18*(22), 2730–2735. https://doi.org/10.1101/gad.308904

(6) Tikka, S., Baumann, M., Siitonen, M., Pasanen, P., Pöyhönen, M., Myllykangas, L., Viitanen, M., Fukutake, T., Cognat, E., Joutel, A., & Kalimo, H. (2014). CADASIL and CARASIL. *Brain pathology (Zurich, Switzerland)*, *24*(5), 525–544. https://doi.org/10.1111/bpa.12181

(7) Manini, A., & Pantoni, L. (2021). CADASIL from Bench to Bedside: Disease Models and Novel Therapeutic Approaches. *Molecular neurobiology*, *58*(6), 2558–2573. https://doi.org/10.1007/s12035-021-02282-4

(8) Guey, S., Mawet, J., Hervé, D., Duering, M., Godin, O., Jouvent, E., Opherk, C., Alili, N., Dichgans, M., & Chabriat, H. (2016). Prevalence and characteristics of migraine in CADASIL. *Cephalalgia : an international journal of headache*, *36*(11), 1038–1047. https://doi.org/10.1177/0333102415620909

(9) Dichgans M. (2009). Cognition in CADASIL. *Stroke*, *40*(3 Suppl), S45–S47. https://doi.org/10.1161/STROKEAHA.108.534412

(10) Maclean, A. V., Woods, R., Alderson, L. M., Salloway, S. P., Correia, S., Cortez, S., & Stopa, E. G. (2005). Spontaneous lobar haemorrhage in CADASIL. *Journal of neurology, neurosurgery, and psychiatry*, *76*(3), 456–457. https://doi.org/10.1136/jnnp.2004.042564

(11) Moreton, F. C., Razvi, S. S., Davidson, R., & Muir, K. W. (2014). Changing clinical patterns and increasing prevalence in CADASIL. *Acta neurologica Scandinavica*, *130*(3), 197–203. https://doi.org/10.1111/ane.12266

(12) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, 2013.

(13) Depression: The Treatment and Management of Depression in Adults (Updated Edition).

National Clinical Practice Guideline 90. National Institute for Health & Clinical Excellence. http://guidance.nice.org.uk/CG90 (Accessed on July 18, 2011).

(14) Rothschild, A. J., Winer, J., Flint, A. J., Mulsant, B. H., Whyte, E. M., Heo, M., ... & Meyers, B. S. (2008). Study of Pharmacotherapy of Psychotic Depression (STOP-PD) Collaborative Study Group Missed diagnosis of psychotic depression at 4 academic medical centers. *J Clin Psychiatry*, *69*(8), 1293-1296.

(15) Jääskeläinen, E., Juola, T., Korpela, H., Lehtiniemi, H., Nietola, M., Korkeila, J., & Miettunen, J. (2018). Epidemiology of psychotic depression - systematic review and meta-analysis. *Psychological medicine*, *48*(6), 905–918. https://doi.org/10.1017/S0033291717002501

(16) Miller, F., & Chabrier, L. A. (1987). The relation of delusional content in psychotic depression to life-threatening behavior. *Suicide & life-threatening behavior*, *17*(1), 13–17. https://doi.org/10.1111/j.1943-278x.1987.tb00058.x

(17) Park, J. H., Jeon, B. H., Lee, J. S., Newhouse, P. A., Taylor, W. D., Boyd, B. D., Kim, K. W., & Kim, M. D. (2017). CADASIL as a Useful Medical Model and Genetic Form of Vascular Depression. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*, *25*(7), 719–727. https://doi.org/10.1016/j.jagp.2017.03.013