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5-year Progression of CADASIL: A Case Report

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Abstract: A female patient in her 40's of mixed Chinese-Indian ancestry was referred to our neurology clinic for frequent migraine with aura and CADASIL. She had been treated for acute encephalopathy in 2014. The incident led to her CADASIL diagnosis and later retinitis pigmentosa, both rare conditions. Initial clinical assessment showed moderate severity of migraine and normal cognitive function. As there is no specific treatment recommended for CADASIL, the patient was maintained on pharmacological therapies for secondary prevention of ischaemic stroke, treatment of seizure, symptomatic treatment for migraine and a cholesterol-lowering drug. A supplement containing Vitamin E (tocotrienols) was recommended. During the ensuing 5-years, there were no further neurovascular incidents and her migraine went into full remission.

Keywords: CADASIL; tocotrienols; vitamin E; stroke

1. Introduction

In 1955, the neurologist, van Bogaert, was probably the first to identify inherited multi-infarct dementia[1]. In 1993, it was genetically identified as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarctions and Leukoencephalopathy (CADASIL)[2]. In middle-aged adults with a family history of stroke or dementia, the most common clinical presentation is migraine with aura, small subcortical strokes, or cognitive impairment[3].

CADASIL is caused by highly stereotyped NOTCH3 gene mutations that result in pathological accumulation of the extracellular NOTCH3 protein domain ($Notch3^{ECD}$)[4]. Clinical manifestations of CADASIL include migraine with aura, subcortical ischaemic events, mood disturbances, apathy, and cognitive impairment. The occurrence of these symptoms varies with age and duration of disease[5–8]. Migraine with aura is often the first clinical manifestation[9]. It

was reported that there is 75% chance of CADASIL patients experiencing migraine, 90% of them with aura[10]. The average age for women was 26 years when first presenting with symptoms[11]. Ischaemic events such as transient ischaemic attacks and ischaemic strokes are the most common manifestations and usually occur in the fifties age range with an estimated incidence of 10.4 per 100 patient-years[12]. CADASIL patients with stroke are more likely to develop between two and five recurrent strokes over the years, which progressively lead to other complications[5,6,8]. Cognitive impairment, which is the second most frequent manifestation, can also be seen in almost all patients beyond 50 years of age. Previous study showed that CADASIL is dominated by early executive dysfunction and was observed in all individuals aged 35–73 years[13].

CADASIL can be seen as a pleomorphic disease: in different families, the dominant manifestations may vary; and in individuals of the same family, the clinical picture and functional course can also often differ[14]. In the final stages, individuals are usually bedridden, apathetic, and completely dependent. Time to death is also highly variable ranging from 10 to 30 years and is usually caused by accumulation of morbidities and clinical complications related to infection and immobility[15].

There is currently no specific treatment recommended for CADASIL. Management of the disease consists of drug therapy for symptomatic migraine, epilepsy, and psychiatric problems such as depression. Patients are advised to quit smoking and are treated with aspirin to reduce the risk of stroke, while other vascular risk factors such as diabetes, hypertension, and hyperlipidaemia, are aggressively treated. Patients with significant cognitive deficits are treated with centrally acting cholinesterase inhibitors or other drugs for neurodegenerative disorders.

2. Case History

A female of mixed-lineage (Chinese and Indian) in her 40’s, with a family history of young stroke and migraine, was referred to our clinic for chronic migraine with aura and CADASIL, which had been diagnosed one year earlier.

Based on her recent medical history, she was treated for acute reversible focal encephalopathy and was responsive to steroid therapy in the year 2014 (Figure 1). Her first incident was followed with a second hospitalisation within 2 weeks of discharge after which she was diagnosed with CADASIL and retinitis pigmentosa, both rare conditions. An MRI brain scan during the first hospitalisation showed white matter hyperintensities in the periventricular and anterior temporal regions. The second MRI brain scan revealed additional hyperintensity over the left occipital lobe on diffusion-weighted imaging, suggesting a transient ischaemic attack. The MRI findings and neurovascular incidents, combined with her history of migraine and family history of young stroke, were hallmarks of CADASIL. Her diagnosis was confirmed genetically, which showed the R110C mutation in the exon 3 of the NOTCH3 gene. She was the index case in her family and was first profiled by Toh *et al*.[16]

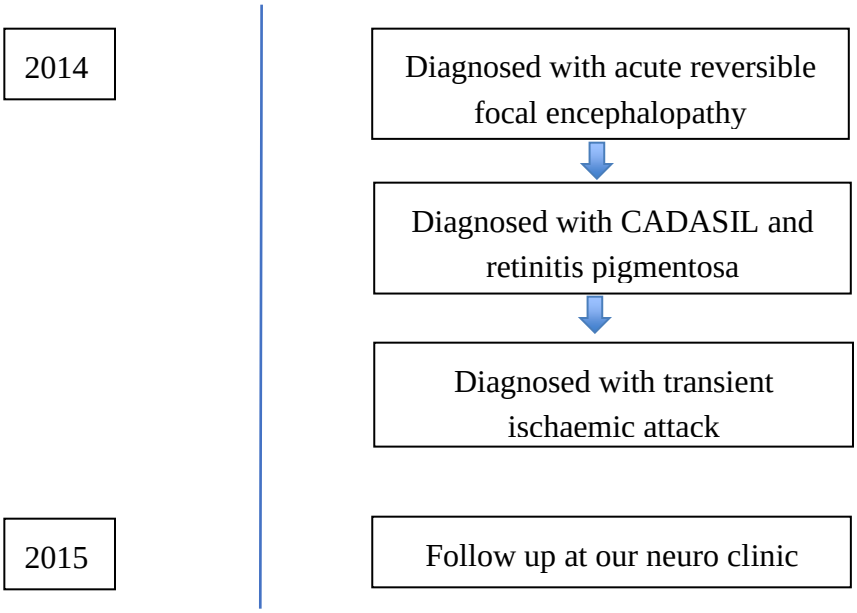

Figure 1. Patient's medical history timeline.

She has a family history of young stroke and dementia (grandmother, uncle, aunt, and mother). Of her two brothers, one is asymptomatic, while the elder brother, currently in his 50's, has migraines, stroke, signs of cognitive impairment, and MRI brain anomalies suggestive of CADASIL. Similar clinical presentations were observed in the elder brother too. He has had migraines since his 20's. The migraine attacks occur once every three to four months, presenting as left-sided headaches with vomiting and hand numbness. In 2015, he experienced leg weakness and numbness which gradually improved. MRI scans showed multiple cerebral white matter lesions with active lesions in the left frontal-parietal lobe. However, the magnetic resonance angiography study was normal and the computerized tomography (CT) brain scan showed no sign of stroke. He was admitted to a hospital in 2017 and treated for possible transient ischaemic stroke. The CT brain scan did not show any new stroke. He did not undergo confirmatory tests for CADASIL or retinitis pigmentosa.

The patient had suffered from chronic migraine with aura since she was in her mid-20s. Her migraine usually started as left-sided headaches with throbbing pain. The condition was cyclical in episodes. She would experience two to three episodes of headache with pain in a week followed by a six-month pain-free period; until it reoccurred again.

On interview, she was found to be a health-conscious person and very organized in managing her family and her children's education. The patient had no history of tobacco or alcohol use in any form.

The patient was assessed annually over the last 5 years, following her first visit in 2015. Initial assessments indicated she had normal cognitive function with moderate impact from her

migraine attacks. The Headache Impact Test (HIT) score was 57 and the Montreal Cognitive Assessment (MoCA) score was 29.

Initial examinations showed she had a normal body mass index (21.1 kg/m^2), which was well maintained through the 5 years of follow-up. She also has hypercholesterolaemia which is managed with Rosuvastatin (10 mg per day). Her initial neurological examinations were unremarkable.

The cognitive assessments, namely, MMSE, MoCA, Trail Making Test, and Clock Drawing Test, indicated she maintained normal cognitive function 5 years into her initial diagnosis with CADASIL (Table 1).

The patient was already on medication for secondary prevention of stroke since her neurovascular incidents of CADASIL coma 1 year earlier. During the 5-year follow up period, her condition was well-controlled with the prescribed drugs, namely, Propranolol 30 mg twice per day, Levetiracetam 750mg twice per day, Clopidogrel 75 mg once per day, Rosuvastatin 10mg once per day, and Folic Acid 5mg once per day. During the initial assessment, it was recommended that the patient take a vitamin E supplement (tocotrienols), which could be sourced over the counter from pharmacies. Supplementation with tocotrienols was recommended for general well-being and such use is supported with studies documenting benefits in preventing progression of white matter lesion and stroke lesions[17–20]. The patient took tocotrienols (200 mg) daily throughout the 5-year follow-up period. There was no change to the medications taken by the patient during the 5 years of follow-up and the patient remained compliant with regard to the tocotrienols supplementation as recommended. There were no further medical incidents that required any acute or long-term intervention. The patient had been followed for 5 years. Approximately 12 months after the first visit, the patient reported sustained improvement of migraine symptoms. She was scheduled to return for follow-up visits once a year. Because she had shown remarkable regression of the migraine, continued use of tocotrienols supplement and maintenance of her medications were recommended, with clinical assessments conducted annually (Table 1).

Cognitive assessment using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) at baseline, Year 1, Year 2, Year 3, Year 4, and Year 5 showed no cognitive impairment. Additional executive function assessment at Year 2, Year 3, Year 4, and Year 5 using Clock Drawing Task (CLOX) and Trail Making Test (TMT) not only showed no impairment in executive function but a slight improvement of it.

The Headache Impact Test (HIT-6) conducted at Initial visit, Year 1, Year 2, Year 3, Year 4, and Year 5 showed a marked reduction of headache incidence and a positive impact on daily living.

The patient continued to be monitored and appears stable with no further deficits at the time of this writing.

Table 1. Assessment outcomes (scores) at baseline, Year 1, Year 2, Year 3, Year 4, and Year 5.

Assessment	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Cognitive assessment						
Mini-Mental State Examination (MMSE)	-	29	30	30	29	30
Montreal Cognitive Assessment (MoCA)	29	27	28	27	29	28
Trail Making Test-A (TMT-A)	-	-	77	52	64	45
Trail Making Test-A (TMT-B)	-	-	95	96	131	80
Clock Drawing Task-1 (CLOX-1)	-	-	15	15	15	15
Clock Drawing Task-1 (CLOX-2)	-	-	15	15	15	15
Migraine assessment						
Headache Impact Test (HIT-6)	57	36	36	36	36	36

3. Discussion

CADASIL is a monogenic type of small vessel cerebral disease, characterized by a high prevalence of microbleeds and high ischaemic stroke frequency[21]. The patient had experienced a transient ischaemic attack before. Among patients with the same condition, one in five will have a high risk of subsequent stroke[22]. Antiplatelet therapy with aspirin and clopidogrel is an established long-term regime and a cornerstone of secondary stroke prevention[23]. Previous literature also showed an 8% risk reduction of ischaemic stroke among those who take a vitamin E supplement[24]. Therefore, it was recommended to the patient that she adds tocotrienols supplementation to her medication.

Cognitive impairment affects about 60% of patients with CADASIL. Most patients develop significant cognitive deficits as a result of debilitating stroke. Initially, cognitive impairment manifests as mild executive and visuospatial deficits, psychomotor retardation, and apathy. In the absence of significant vascular events, subtle cognitive deficits may develop and do not appear to be associated with the severity of brain lesions, as seen in the MRI findings[25]. Working and short-term memory defects also appear perniciously before the first onset of symptomatic ischaemic episodes followed by the main manifestations of CADASIL, such as abulia and other executive dysfunctions[26]. The patient in this case study showed no further deficit in cognitive function or executive performance over the 5 years of follow-up.

In patients with CADASIL, 75.3% present with migraine and 89.9% have migraine accompanied by aura[27]. Although the patient was prescribed propranolol for migraine prophylaxis, migraine persisted with moderate impact on her quality of life. The symptoms reduced approximately 6 months after starting on the Vitamin E (tocotrienols) and completely disappeared by the end of 1 year of supplementation. Vitamin E (tocotrienols) prevents arachidonic acid release and the conversion of arachidonic acid to prostaglandin by acting on the phospholipase A2 and cyclooxygenase enzymes[28]. This anti-prostaglandin property can effectively reduce pain and related symptoms of migraine. A study showed that Vitamin E reduced (a) the number of migraine and headache days per month by three; (b) migraine duration; (c) headache pain scores; and (d) medication use[29].

During the follow-up at year 1, the patient also reported observing less hair loss and a higher rate of hair growth. This is consistent with a previous study that showed tocotrienols supplementation increased hair growth 34.5% between the baseline and the end of the 8-month study[30]. Oxidative stress in the scalp was reported to be associated with hair loss[31]. Thus, improved hair growth could be ascribed to the potent anti-oxidant activities of vitamin E.

4. Conclusions

In conclusion, this case report shows a non-progressing CADASIL patient with stable cognitive performance and general well-being over 5 years of follow-up. Vitamin E (tocotrienols) supplementation could be given as an adjunct treatment for CADASIL patients and in this particular case it was determined to be safe when used with other concomitant medications. The safety of the treatment was ultimately evidenced, in part, by the fact that the patient reported no adverse effects. Anecdotal observations from the patient indicate that there is a benefit to general health from continuous supplementation with a potent anti-oxidant such as tocotrienols. The regression of chronic migraine symptoms observed with concurrent initiation of tocotrienols supplementation is worth further investigation in randomised controlled trials to confirm the effects.

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