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A Case Series of Monogenic Strokes in A Tertiary Care Centre

Case Series

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Abstract

Monogenic strokes are a rare but significant cause of stroke in young individuals and often present with distinct clinical and radiographic features. This case series describes three young patients with stroke caused by different monogenic disorders: CADASIL (NOTCH3 mutation), Werner syndrome (WRN gene mutation), and congenital contractural arachnodactyly (FBN2 mutation). Each case highlights unique clinical and imaging characteristics, emphasizing the importance of genetic testing in young stroke patients, particularly in the absence of traditional vascular risk factors. Early recognition and diagnosis of monogenic strokes can guide appropriate management and genetic counseling, underscoring the need for increased awareness and consideration of genetic causes in young stroke patients.

Keywords: Monogenic Stroke; Cerebral Small Vessel Disease; Genetics

Introduction

Stroke is one of the leading causes of death and long-term disability worldwide. The pathogenesis of stroke is multifactorial. Cerebral small vessel disease (CSVD) refers to a syndrome of clinical, neuroimaging, and neuropathological findings arising from pathological processes affecting cerebral perforating arteries, arterioles, capillaries, and venules [1]. The underlying etiology varies, and some causes are genetic in origin.

Monogenic small vessel diseases are responsible for approximately 1-5% of strokes, particularly among young individuals [2]. “Monogenic stroke” refers to stroke caused by a rare single-gene mutation or disorder. These disorders may present with transient ischemic attacks, lacunar infarcts, cognitive decline, psychiatric manifestations, and dementia. The identification of genes implicated in such disorders has enhanced understanding of disease mechanisms and facilitated the development of disease models.

In this case series, we describe the clinical presentations, imaging findings, and genetic basis of three young patients with monogenic stroke.

Case 1

A 40-year-old male presented with progressive cognitive decline, behavioral changes and spastic paraparesis for one year. He had a past history of migraine and a positive family history of similar complaints in his father.

On examination his BP was 140/90 mmHg. Neurological examination revealed bilateral pyramidal signs and executive dysfunction. His routine blood investigations (CBC, RFT, LFT, ESR, CRP) and autoimmune panel (ANA, APLA) were within normal limits. His MRI brain (Figure 1) showed T2 FLAIR hyper intense lesions involving external capsule and periventricular leucomalacia with hypertensive microangiopathy.MR Brain angiogram was normal.

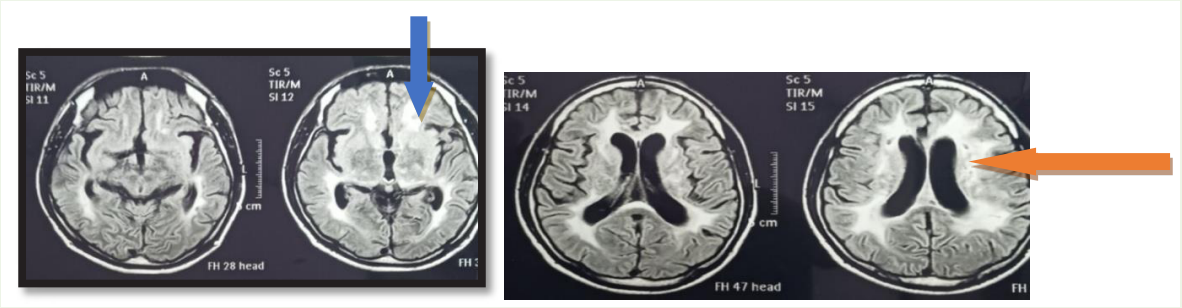

Figure 1: MRI brain showing T2/FLAIR hyper intense lesions involving external capsule (blue arrow) and periventricular leukomalacia (red arrow).

Considering the positive family history, history of migraine and characteristic MRI findings genetic analysis was performed which revealed NOTCH 3 mutation consistent with CADASIL.

Case 2

A 37 year old male with hypertension for three years presented with recurrent stroke episodes. The first episode consisted of sudden onset left sided weakness that resolved within a few hours, followed four months later by dysarthria.He also had a history of cataract requiring surgery. His father had a history of young onset left hemiparesis.

On clinical examination his blood pressure was elevated (180/100mmHg). Neurological examination showed left UMN facial nerve palsy, bilateral pyramidal signs and extensor plantar responses. Routine laboratory investigations including autoimmune workup (ANA, ANA blot, APLA) were within normal limits. Two dimensional ECHO showed evidence of hypertensive heart disease. USG abdomen with renal Doppler study was normal.

MRI brain (Figure 2) revealed T2/ FLAIR hyper intense white matter lesions involving the periventricular, external capsule and anterior temporal pole. His MR brain angiogram was normal.

In view of young age, positive family history and characteristic MRI findings clinical exome sequencing was performed and revealed WRN gene mutation suggestive of Werner syndrome.

Case 3

A 19 year old boy presented with six episodes of transient left sided weakness over one month, with each episode lasting approximately 30 minutes and complete recovery afterward. There was no significant past or family history.

On examination his vitals were stable. General examination revealed marfanoid features including joint hyper mobility, high arched palate and arm span to height ratio greater than one. Neurological examination showed left pronator drift, brisk reflexes and an extensor plantar response on the left side.

His routine lab investigations (CBC, RFT, LFT, ESR, CRP) including autoimmune profile (ANA, APLA), serum homocysteine were normal.

MRI brain (Figure 3) demonstrated an acute ischemic infarct in the right frontal lobe with diffusion restriction. MR angiogram was normal.

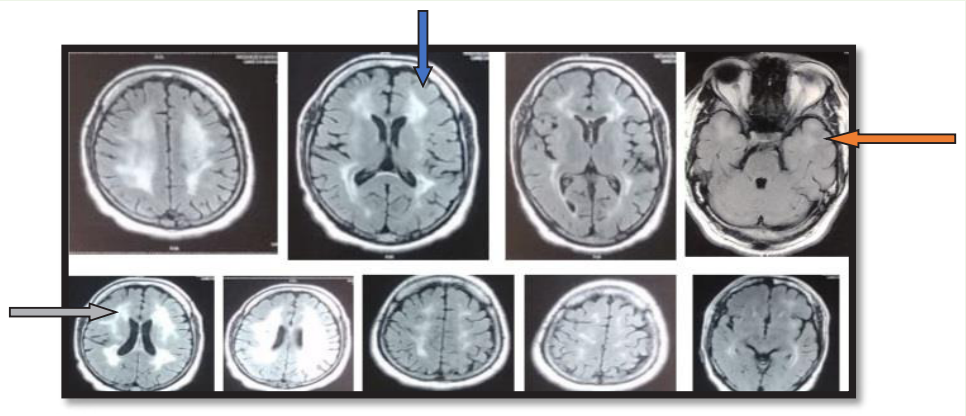

Figure 2: MRI brain showing T2/ FLAIR hyperintense lesions involving the external capsule (blue arrow), anterior temporal pole (red arrow), and periventricular white matter (green arrow).

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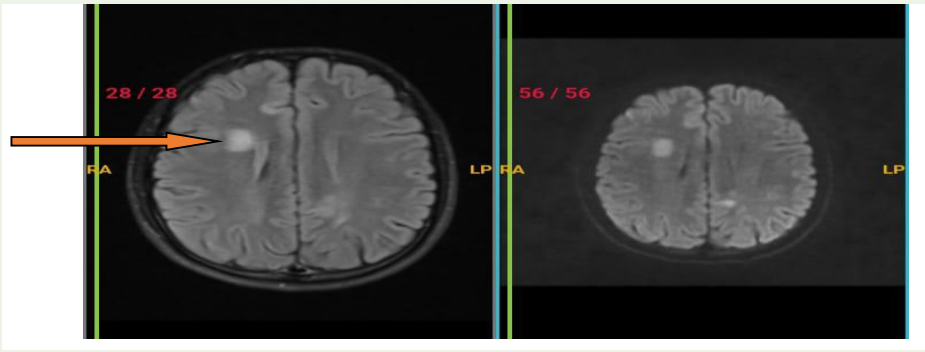

Figure 3: MRI brain showing a T2/FLAIR hyperintense lesion in the right frontal lobe with diffusion restriction, suggestive of acute ischeimic infarction.

Table 1: Summary of Clinical Features, MRI Findings and Genetic Analysis

Sl.No	AGE	SEX	CLINICAL FEATURES	CO-MORBIDITIES	MRI BRAIN FINDINGS	GENETIC ANALYSIS
1	40	M	Behavior changes, spastic ataxia	Hypertension Migraine Positive family history	Hypertensive microangiopathy with periventricular leucomalacia with external capsule involvement	NOTCH 3 gene mutation (chromosome19)-CADASIL
2	37	M	Recurrent stroke, left hemi paresis	Cataract, Hypertension Positive family history	White matter hyper intensities involving periventricular region, temporal pole and external capsule	WRN gene mutation (chomosomer8p12)-Werner Syndrome
3	19	M	Recurrent transient left hemi paresis	Marfanoid features	Acute infarct in right frontal lobe	FBN2 gene mutation (chromosome 5)-Congenital contractural arachnodactyly

In view of the marfanoid habitus and recurrent transient ischemic episodes genetic testing was performed which revealed an FBN2 missense mutation suggestive of contractural arachnodactyly.

Discussion

Stroke remains a major cause of mortality and long-term disability worldwide. It is a heterogeneous condition resulting from a complex interplay of environmental and genetic factors. The TOAST classification categorizes ischemic stroke into five etiological subtypes: large artery atherosclerosis, small vessel disease, cardio embolism, stroke of other determined etiology, and stroke of undetermined etiology [3].

Genetic causes should be considered in young stroke patients, especially when conventional vascular risk factors, systemic disorders, and cardiac etiologies are absent. The most common monogenic disorders associated with stroke include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Fabry disease, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), COL4A1-related disorders, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), and hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS).

CADASIL is the most common monogenic cerebral small vessel disease and is caused by cysteine-altering pathogenic variants in the NOTCH3 gene located on chromosome 19. More than 280 pathogenic NOTCH3 mutations have been described, including deletions, duplications, and splice-site mutations. Approximately 95% are pathogenic missense variants. Clinical manifestations include migraine, ischemic episodes, cognitive impairment, psychiatric disturbances, and acute reversible encephalopathy [4], many of which were observed in our patient. MRI brain typically demonstrates subcortical infarcts and white matter hyperintensities involving the anterior temporal lobe and external capsule, which are characteristic imaging findings. Diagnosis is confirmed by genetic testing, and treatment remains largely supportive.

Werner syndrome is a rare autosomal recessive disorder caused by loss-of-function mutations in the WRN gene on chromosome 8p12. It is characterized by features of premature aging, including early cataracts, premature atherosclerosis, osteoporosis, and type 2 diabetes mellitus [5]. Diagnosis is established through genetic evaluation, while treatment is primarily supportive and focused on management of vascular risk factors.

Congenital contractural arachnodactyly (CCA) exhibits a broad phenotypic spectrum. Classical CCA is characterized by arachnodactyly, flexion contractures involving multiple joints, kyphoscoliosis, marfanoid habitus, highly arched palate, muscular hypoplasia, and characteristic crumpled ears [6]. The clinical phenotype can vary considerably within affected families. Although cerebrovascular involvement is uncommon, connective tissue abnormalities may predispose affected individuals to vascular complications.

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Conclusion

Monogenic diseases are rare but important causes of stroke in young individuals and are frequently under diagnosed. Due to overlapping phenotypes and marked intrafamilial variability, diagnosis can be challenging. However characteristic clinical features and neuroimaging findings may provide important clues to the underlying genetic etiology.

Although genetic testing is expensive, it should be considered as part of diagnostic workup in young patients with cerebrovascular events, particularly when conventional vascular risk factors are absent or when there is a positive family history. Early diagnosis facilitates appropriate management, genetic counseling and prognostication.

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