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Review Article

Hereditary cerebral small vessel disease and stroke

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ABSTRACT

Cerebral small vessel disease is considered hereditary in about 5% of patients and is characterized by lacunar infarcts and white matter hyperintensities on MRI. Several monogenic hereditary diseases causing cerebral small vessel disease and stroke have been identified.

The purpose of this systematic review is to provide a guide for determining when to consider molecular genetic testing in patients presenting with small vessel disease and stroke.

CADASIL, CARASIL, collagen type IV mutations (including PADMAL), retinal vasculopathy with cerebral leukodystrophy, Fabry disease, hereditary cerebral hemorrhage with amyloidosis, and forkhead box C1 mutations are described in terms of genetics, pathology, clinical manifestation, imaging, and diagnosis.

These monogenic disorders are often characterized by early-age stroke, but also by migraine, mood disturbances, vascular dementia and often gait disturbances. Some also present with extra-cerebral manifestations such as microangiopathy of the eyes and kidneys. Many present with clinically recognizable syndromes.

Investigations include a thorough family medical history, medical history, neurological examination, neuroimaging, often supplemented by specific examinations e.g of the of vision, retinal changes, as well as kidney and heart function. However molecular genetic analysis is the final gold standard of diagnosis.

There are increasing numbers of reports on new monogenic syndromes causing cerebral small vessel disease.

Genetic counseling is important. Enzyme replacement therapy is possible in Fabry disease, but treatment options remain overall very limited.

Contents

Abbreviations: AD, Alzheimer's disease; APP, Aβ precursor protein; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CRV, cerebroretinal vasculopathy; CST3, cystatin C gene; EGF-like, epidermal-growth-factor-like; ERT, enzyme replacement therapy; GOM, granular osmiophilic material; HANA, Chereditary angiopathy with nephropathy, aneurysm, and muscle cramps; HCHWA, hereditary cerebral hemorrhage with amyloidosis; HCHWA-D, hereditary cerebral hemorrhage with amyloidosis-dutch type; HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; HRV, hereditary vascular retinopathy; HSA, hereditary systemic angiopathy; ICH, Intracerebral hemorrhage; MRI, magnetic resonance imaging; MRI-MRA, magnetic resonance imaging–magnetic resonance angiography; RVCL, retinal vasculopathy with cerebral leukodystrophy; SVD, small vessel disease; TIA, transient ischemic attacks; USA, United States of America; WM, white matter; WML, white matter lesion.

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1. Introduction

Hereditary small vessel diseases are a minor part of cerebral small vessel disease (SVD), which is known to cause ischemic and hemorrhagic strokes and dementia [1]. About 25% of ischemic strokes are attributed to small vessel disease [2].

The recognition of cerebral SVD depends on correct neuroimaging. With the increasing availability, quality and decreasing cost of magnetic resonance imaging (MRI) patients suffering from SVD are more likely to be identified [1].

Brain SVD is recognized by focal ischemic lesions or lacunes and T2-weighted white matter (WM) hyperintensities on MRI [3]. The term leukoaraiosis is often used to describe this finding. The most common cause of sporadic small vessel disease is arteriosclerosis [1]. Known risk factors include age, hypertension, hyperlipidemia, high body mass index, high fasting glucose level, and smoking [4]. Other causes of cerebral SVD includes sporadic cerebral amyloid angiopathy, amyloidosis, inflammatory- and immune-mediated SVD, venous collagenosis, and monogenic, hereditary disorders [1].

Preceding or in relation to stroke or dementia, patients with SVD may suffer from motor and cognitive executive slowing, forgetfulness, dysarthria, mood changes, urinary symptoms, and short-stepping gait [5]. The current treatment of sporadic SVD includes symptomatic treatment as well as secondary preventive measures such as anti-thrombotic treatment [1]. Monogenic disorders are important to identify from SVD because of the possibility of different treatment options and the possibility of genetic counseling. Knowledge of monogenic SVD may provide understanding of which pathways are affected in sporadic SVD.

Stroke incidence due to monogenic disorders is unknown and may be underdiagnosed; however monogenic disorders are estimated to constitute approximately 5% of all strokes [6]. Recent advances have discovered the genetic causes of many cerebral SVD by genetic linkage studies, genome wide association studies, and candidate gene approaches [7]. However the genetic loci of several known familial SVD of the brain have not been identified, for instance hereditary multi-infarct dementia of the Swedish type [8]. Future research is likely to uncover more genetic causes of cerebral SVD [6].

A history of stroke or dementia in the family of a patient presenting with cerebral SVD and stroke raises suspicion of a genetic disorder. A young age of onset or absence of risk factors in elderly patients with stroke supports suspicion [9].

The purpose of this review was to provide current information on monogenic hereditary cerebral small vessel diseases concerning clinical manifestations, neuroimaging, and genetic cause. Only diseases with known genetic loci and increased stroke occurrence are included.

In the discussion the clinical approach to a stroke patient suspected of a monogenic disorder is reviewed. Seven monogenic disorders were identified; Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL), Collagen-type(IV)-