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Hereditary forms of subcortical small vessel disease. The need for registries

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Abstract

Hereditary forms of subcortical small vessel disease (SSVD) leading to vascular cognitive impairment (VCI) comprise a heterogeneous group of rare genetic disorders, suitable for the study of the mechanisms and relationship between SSVD and VCI. Since these disorders are rare, better knowledge of their clinical, genetic, imaging and biochemical characteristics may be achievable only through registries which additional may help in better recruitment of patients for studies. A great amount of our current knowledge on these disorders has been gained through registries and data bases. International registries may further help in expanding our experience in epidemiological or even preventive and therapeutic aspects of hereditary SSVD.

Introduction

Hereditary cerebral angiopthies comprise a heterogeneous group of rare genetic disorders [1] leading to ischemic and/or hemorrhagic stroke, subcortical small vessel disease (SSVD) and vascular cognitive impairment (VCI) [2]. Among many others, the most widely known of these disorders are cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoancepahlopathy (CADASIL) due to *NOTCH3* mutations [3], disorders due to mutations of the genes encoding either alpha1 or alpha2 chain of collagen type IV (*COL4A1*, *COL4A2*) [4] and mutations of the *HTRA1* gene, including cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) [5,6]. Sporadic cases of SSVD due to classical cardiovascular risk factors, such as hypertension, diabetes, smoking and dyslipidemia are much more common [2,7]. However, up to 2/3 of sporadic SSVD patients have additional Alzheimer's disease pathology [8] and such mixed cases may be less suitable for studying pure VCI. On the other hand, hereditary forms of SSVD constitute a pure population of patients (or clear animal models) [9], suitable for the study of the relationship between SSVD and VCI [10,11]. Since hereditary forms of SSVD are rare, better knowledge of these disorders and recruitment of patients for studies may be achievable only through registries [12,13]. Such registries may prove helpful in understanding various genetic, clinical and epidemiological parameters of these disorders.

Cadasil

It has been shown that archetypal *NOTCH3* mutations may be 100-fold more frequent than previously thought, indicating that some mutations may result in mild phenotypes, sometimes clinically unrecognized [14]. Indeed, patients with a later onset of stroke [15], with a "benign" form of the disease presenting with stroke at the 8th decade [16], or with a normal-appearing 3T MRI at the 4th decade [17] are increasingly being recognized. Thus, it seems that the epidemiology of CADASIL is changing, characterized by an increasing prevalence and a relatively less severe presentation or a more favorable natural history and, patients from the Duch CADASIL registry and the neurovascular genetics clinic in Scotland were involved in such studies [14,15]. Better understanding and suspicion of the disease, resulting in recognition of relatively "benign" cases may be one cause of the above change. Additionally, it is now recognized that the classical cardiovascular risk factors may adversely affect CADASIL progression [18-23]. It is possible that control of these risk factors, which is currently strongly recommended [11,24], contributed in a more favorable prognosis of the disease [25].

COL4A1/A2-related disorders

The phenotypic spectrum of *COL4A1/A2*-related disorders is continuously expanding [4]. Recently, epilepsy-predominant phenotypes have been recognized [26]. Late onset cases, asymptomatic cases, sporadic cases, *de novo* mutations and coexistence of multiple risk factors have also been described [4,27]. Furthermore, several variants of *COL4A2* may be associated with sporadic SSVD resulting in deep intracerebral hemorrhage [28], while *COL4A1/A2* variants may be associated with coronary heart disease in the young [29].

HTRA1–related disease

It is now recognized that some heterozygous *HTRA1* mutations lead to an autosomal dominant form of SSVD [30,31]. This may present

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with a relatively less severe phenotype in many (but not all) patients compared to the recessive form (CARASIL) [32] and seems to be more frequent than the later, accounting for up to 5% of hereditary SSVD [30,32].

Thus, during the last 10-15 years cumulative data not only from registries [12,13], but also from specialized centers, databases and established consortia [4,26,33,34] expanded our knowledge on these disorders. Furthermore, they provided evidence about the relative frequency of these disorders among inherited SSVD. It seems that the most frequent is CADASIL accounting for 58% of patients, followed by *COL4A1/A2* mutations (at least 13%) and heterozygous forms of *HTRA1* mutations [4,30,32,33].

Our local registry

In the 1st department of Neurology of the National and Kapodistrian University of Athens, Greece, a local registry named "Migraine and Specific Vasculopathies Registry" was launched in 2011, for patients suffering of hereditary SSVD and hereditary forms of migraine. Clinical, genetic, neuropsychological, imaging and biochemical data are registered, including data on dementia biomarkers in cerebrospinal fluid (such as amyloid-beta, total tau and phospho-tau proteins). Since 2011, we have identified and published 3 novel families with CADASIL, 2 of which had atypical features [35,36] and one had oligosymptomatic presentation [37]. Thus, we identified one new CADASIL family every 2.5 years. We have also described a new oligosymptomatic patient [38] from a 4th CADASIL family previously described in our department [39]. The above families consist of at least 12 alive CADASIL patients. A family with a phenocopy of *COL4*-related disease (but no *COL4A1/A2* mutation) was also described [40]. Additionally we have been involved in the description of the 1st patient with heterozygous *HTRA1* mutation in Greece [41].

Conclusion

Although local, since our department is a tertiary referral center, the registry may cover a population much wider than the one expected from geographical boundaries and the same holds trough for all local registries in academic centers. However, nation-wide registries supported by many collaborating specialized centers are preferable, while international registries may be required.

Authorship

George P. Paraskevas: conception and design, acquisition and interpretation of literature data, drafting, final approval, guarantor.

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