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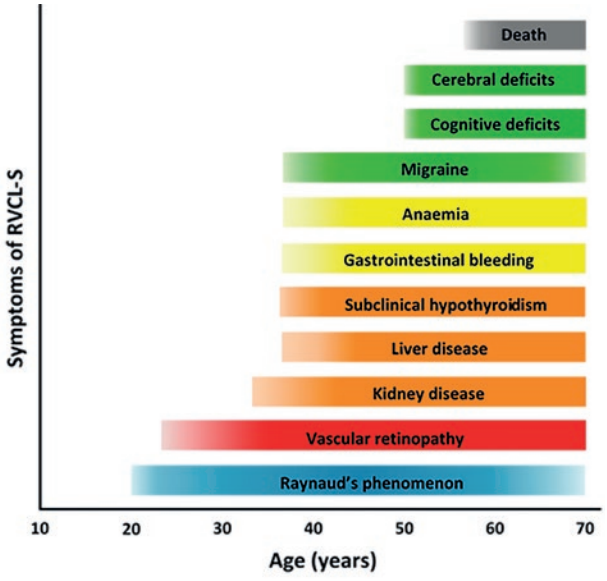
LETTER TO EDITOR

Dear Editor,

Recently, Monroy-Jaramillo et al.[1] described a new family with a disorder now known as retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S)[2]. RVCL-S is a monogenetic small vessel disease caused by C-terminal frameshift mutations in *TREX1*[3]. The auteurs confirm phenotypic variability in RVCL-S but inaccurately claim a large number of pre-manifest mutation carriers[2]. In general, RVCL-S is often underdiagnosed as not all necessary diagnostic tests are performed. In a large study with 78 patients from 11 unrelated families, neuroimaging reveals white matter lesions with or without nodular enhancement (97%), rim-enhancing mass lesions (84%), and calcifications (52%). Clinical brain symptomatology was found in 90%, including focal neurological deficits (68%), migraine (59%), cognitive impairment (56%), psychiatric disturbances (42%), and seizures (17%). Systemic features included liver disease (78%), anemia (74%), nephropathy (61%), hypertension (60%), Raynaud's phenomenon (40%), and gastrointestinal bleeding (27%)[2] (Fig. 1). Therefore, we advise follow-up with diagnostic laboratory, ophthalmological, and neuro-radiological screening of RVCL-S mutation carriers but strongly object against biopsies because these have no added value. We would like to stress that disease status can be reliably made based on genetic testing and clinical and radiological findings alone. We would strongly argue against withholding a diagnosis to (potential) mutation carriers, especially as this is relevant for their brain, eyes, and systemic condition and, if followed up regularly, may prevent unnecessary invasive tests and allows for timely ophthalmological treatment to prevent blindness at a young age.

Figure 1. Clinical course of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S). Symptoms of RVCL[2,4] derived from cross-sectional investigation of RVCL-S patients (aged 18-65 years). Vascular retinopathy and Raynaud's phenomenon are the earliest symptoms presenting from age 20 onward. Kidney disease becomes manifest from around the age of 35 years, followed by liver disease, anemia, and, in some mutation carriers, migraine and subclinical hypothyroidism, all from age 40. Cerebral and cognitive deficits usually started mildly around age 50, associated with increasing volume of white matter hyperintensities and intracerebral mass lesions, and becoming severe and ultimately lethal around the age of 60-65 years.



REFERENCES

1. Monroy-Jaramillo N, Cerón A, León E, et al. Phenotypic variability in a Mexican mestizo family with retinal vasculopathy with cerebral leukodystrophy and TREX1 mutation p.V235Gfs*6. Rev Invest Clin. 2018;70:68-75.
2. Stam AH, Kothari PH, Shaikh A, et al. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. Brain. 2016;139:2909-22.
3. Richards A, van den Maagdenberg AM, Jen JC, et al. C-terminal truncations in human 3'-5' DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. Nat Genet. 2007;39:1068-70.
4. Pelzer N, Hoogeveen ES, Haan J, et al. Systemic features of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations: a monogenic small vessel disease. J Intern Med. 2018; [Epub ahead of print].

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Dear Editor,

We thank de Boer *et al.* for their valuable comments to our article and for drawing attention to the early manifestations and pre-manifest subjects in retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S)[1]. In our article, we reported phenotypic variability in three related cases and analyzed their large genealogy. The genetic testing identified 15 additional *TREX1* gene mutation carriers, who in the neurological evaluation conducted at that time did not show evident clinical symptoms of RVCL-S, including Raynaud's phenomenon (authors' Fig. 1). The mean age of these pre-manifest relatives was 27.2±7.0 years (median = 25; range = 18-40 years, and 60% aged 18-27 years) thus, most of them had not reached the typical age of onset. Due to financial constraints, no neuroimaging or neuro-ophthalmological clinical studies were performed; therefore, we could not ascertain the absence of vascular retinopathy or subclinical brain signs in some of the older pre-manifest carriers. Vascular retinopathy in RVCL-S becomes apparent in the fourth or fifth decade of life, soon followed by clinical manifestations of progressive focal and global brain disease[1], and according to Stam et al., the mean age at diagnosis is 42.9±8.3 years[2]. Regarding the follow-up of pre-manifest carriers, we agree with de Boer et al., and medical care was offered to all of them at our institution. Since a brain biopsy should only be considered in cases with uncertain imaging findings and negative family history, the molecular test is definitely the gold standard for RVCL-S diagnosis. Finally, in relation to withholding a diagnosis to pre-manifest mutation carriers, the pre-symptomatic diagnosis was offered to at-risk persons, although only 11 relatives accepted. Until now, merely one out of three pre-manifest carriers returned to our hospital to receive his genetic results; in the remaining carriers, delivery of their results was postponed due to depression, highlighting that few people wish to know their genetic status. Since this is a personal decision, we considered ethical to respect the subjects' autonomy, and their right to not to know[3].

REFERENCES

1. Hardy TA, Young S, Sy JS, et al. Tumefactive lesions in retinal vasculopathy with cerebral leucoencephalopathy and systemic manifestations (RVCL-S): a role for neuroinflammation? J Neurol Neurosurg Psychiatry. 2018;89:434-5.
2. Stam AH, Kothari PH, Shaikh A, et al. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. Brain. 2016;139:2909-22.
3. Ochoa-Morales A, Rodríguez-Agudelo Y, Chávez-Oliveros M, et al. Presymptomatic diagnosis in retinal vasculopathy with cerebral leukodystrophy. EC Neurol. 2018;10:771-6.

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