Spectral domain optical coherence tomography in retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations: a monogenic small vessel disease

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Spectral Domain Optical Coherence Tomography in Retinal Vasculopathy With Cerebral Leukoencephalopathy and Systemic Manifestations: A Monogenic Small Vessel Disease

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Background: Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) is a monogenic small vessel disease caused by mutations in *TREX1*. Several organs, including retina and brain, are affected. Analyzing retinal anatomy is increasingly used as a biomarker for ophthalmological and neurological disorders (due to the shared embryological origin of retina and brain). Optical coherence tomography (OCT) provides a noninvasive cross-sectional visualization of optic disc and macula. We aimed to use OCT to investigate retinal layer thickness in RVCL-S.

Methods: Cross-sectional, 17 *TREX1* mutation carriers (34 eyes) and 9 controls (18 eyes) underwent comprehensive ophthalmologic assessment followed by spectral domain OCT for measuring peripapillary retinal nerve fiber layer (pRNFL) thickness and total macular volume (TMV). Secondary outcomes included measuring thickness of individual macular retinal layers and peripapillary sectors. Findings were analyzed using generalized estimating equations to account for intereye correlation.

Results: *TREX1* mutation carriers had decreased pRNFL thickness (median [interquartile range] 76 [60–99] vs 99 [87–108] μm, $P < 0.001$) and TMV (8.1 [7.4–8.5] vs 8.7 [8.4–8.8] mm^3, $P = 0.006$) compared with controls. With the exception of the temporal sector, the thickness of all peripapillary sectors was decreased in *TREX1* mutation carriers. Ganglion cell layer (30 [22–37] vs 39 [36–41] μm, $P < 0.001$) and inner plexiform layer (27 [24–34] vs 34 [31–35], $P = 0.001$) were thinner in *TREX1* mutation carriers. Notably, in 9 of 12 eyes with normal funduscopic examination, retinal thinning was already detected.

Conclusions: RVCL-S, which may serve as a vascular retinopathy model, is associated with retinal thinning in the peripapillary and macular area. OCT findings can potentially serve as early biomarkers for RVCL-S and other vascular retinopathies.

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Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) is a rare monogenic small vessel disease caused by C-terminal truncating mutations in *TREX1* (1,2).

RVCL-S is characterized by progressive vascular retinopathy and focal and diffuse brain dysfunction.

Decreased visual acuity and/or visual field defects due to vascular retinopathy are the most common presenting symptoms of RVCL-S (2). Despite classic onset of disease between ages 35 and 50, early signs of vascular retinopathy without symptomatology have been demonstrated in patients in their early twenties (2,3). Therefore, ophthalmologists play an important role in recognizing this underdiagnosed condition. Vascular retinopathy in RVCL-S is characterized in the early stages by telangiectasia, microaneurysms, and cotton wool spots. Later, perifoveal capillary obliterations and neovascularizations can occur. As the disease progresses, secondary glaucoma and macula edema can develop as complications of retinopathy (2). Fluorescein angiography often shows focal and extended areas of ischemia, capillary obliteration and

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microaneurysms, neovascularization, telangiectasias, and fluorescein leaks. These findings are less likely to be due to a vasculitis but show similarity to diabetic retinopathy (2–4). Ophthalmological treatment is similar to diabetic retinopathy and often involves retinal laser photocoagulation (peripheral retina mostly) and intravitreal anti-vascular endothelial growth factor therapy. Treatment for secondary glaucoma may be required.

Functional tests demonstrated impaired endothelial function consistent with the wide range of other systemic manifestations, including liver and kidney disease, anemia, and Raynaud phenomenon (1,2,5,6). Currently, there are only symptomatic treatment options available, and symptoms can progress rapidly toward middle age resulting in a premature death (2,6). RVCL-S serves as a monogenic model for common vascular retinopathies and brain disorders, such as diabetic retinopathy and vascular dementia.

Currently, no biomarker is available to predict clinical onset or progression of RVCL-S. Nevertheless, treatment can already be necessary before visual defects occur. Therefore, patients need to be followed up by an ophthalmologist to prevent or postpone severe visual complications. The development of new noninvasive tools to evaluate retinal anatomy in patients at risk of vascular retinopathy opens promising avenues for ophthalmologists (7). In addition, analyzing retinal anatomy has been demonstrated to possibly serve as a biomarker for multiple neurodegenerative disorders (8,9). Optical coherence tomography (OCT) provides a noninvasive high-resolution visualization of retinal layers and may thus provide a useful biomarker for neuro-ophthalmological disorders (10).

We aimed to evaluate spectral domain (SD)-OCT findings in RVCL-S, a monogenetic model for vasculopathy in both retina and brain, by investigating the peripapillary and macular regions by measuring the thickness of peripapillary retinal nerve fiber layer (pRNFL) and macular layers.

METHODS

Patients and Controls

For this cross-sectional cohort study, patients with proven RVCL-S *TREX1* mutations were recruited. Participants were aged ≥18 years and provided informed consent. Controls were selected consecutively from an ophthalmological cohort at the Leiden University Medical Center to obtain a similar age and sex distribution. Exclusion criteria were history of diabetes mellitus, age-related macular degeneration, macular dystrophy, eye trauma, primary glaucoma, other optic neuropathies, and media opacity preventing optimal imaging (severe dry eye, cataract, etc.). Controls were excluded if they had (a history of) ocular, systemic, metabolic, or cerebrovascular diseases or were related to patients with RVCL-S. To evaluate using SD-OCT measurements as early biomarkers, eyes without signs of retinopathy were also assessed. The study was conducted in accordance with the Declaration of Helsinki, and ethics committee approval was obtained.

Ophthalmologic Examinations

Mutation carriers (MC) underwent an ophthalmologic examination by a neuro-ophthalmologist (I.C.N.), including slit lamp examination, applanation tonometry, and ophthalmoscopy. Intraocular pressure (IOP) was measured using kinetic applanation tonometry after instillation of topical oxybuprocaine monofree 0.4% and fluorescein dye. Subsequently, pupils were dilated (tropicamide monofree 0.5% and phenylephrine monofree 5.0%). Afterward, color and red-free photographs of optic disc and macula were taken (TRC-50DX; Topcon Europe Medical BV, Capelle a/d IJssel, The Netherlands) and assessed for retinopathy. Controls underwent standard ophthalmologic examination and fundus photography.

Spectral Domain Optical Coherence Tomography

The optic disc and macula were analyzed in both eyes using SD-OCT (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany) with image alignment eye tracking software (TruTrack Active Eye Tracking; Heidelberg Engineering). Software (Heidelberg Eye Explorer v1.9.10.0) rendered retinal images with a minimum resolution of 768 × 768 pixels with field of view set at 30°. The pRNFL was analyzed with a circular scan with a diameter of 3.5 mm centered on the optic disc. Secondarily, sectorial analyses were performed for different peripapillary segments. Macula retinal layers were measured while focusing on the fovea centralis by divided the area into 9 sectors, using a 1-, 3-, and 6-mm grid (11). Individual retinal layers were automatically demarcated, qualitatively assessed, and quantified by segmentation software (Fig. 1B). Primarily, total macular volume (TMV) was measured to evaluate the retina as a whole, and not only macular thinning due to neuronal loss. As secondary outcomes, total macular thickness (TMT) and thickness of the individual macula layers were evaluated. Finally, we evaluated the pattern of retinal thinning. Scans were obtained by blinded examiners in single session. We used the APOSTEL recommendations for reporting (12).

Statistical Analyses

Statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY). Demographics were compared using the Mann–Whitney *U* test and the Fisher exact test. SD-OCT parameters were analyzed using generalized estimating equations (matrix: exchangeable) to account for intereye correlations within participants. To ensure results were not caused by secondary glaucoma or photocoagulation treatment in the scanned region, we conducted separate analyses for primary outcomes after exclusion of affected eyes. A P value of <0.05 was considered significant.

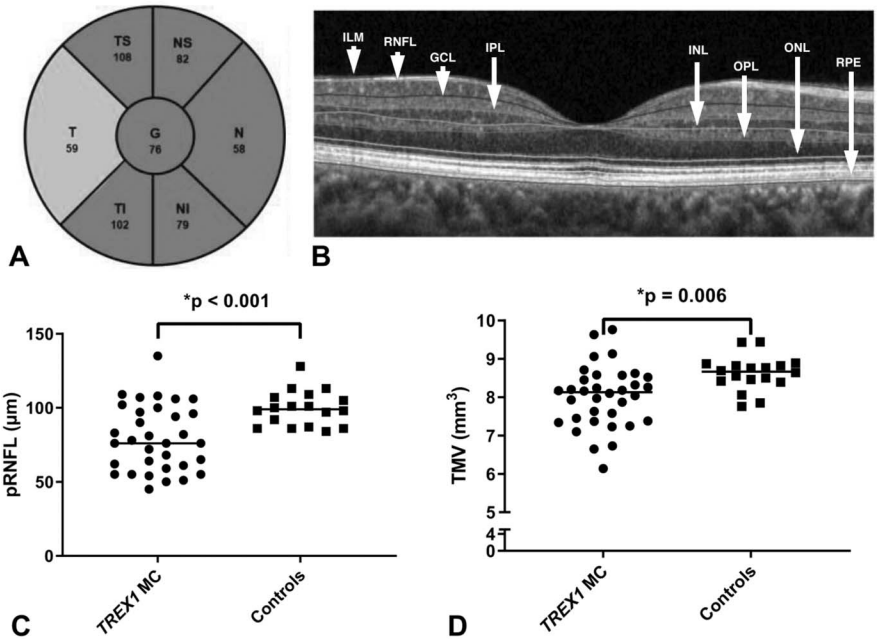

FIG. 1. Spectral domain optical coherence tomography measurements in *TREX1* mutation carriers. Median of all mutation carriers' peripapillary retinal nerve fiber layer (pRNFL) thickness per sector (dark gray indicates decreased thickness) (**A**). Individual macular layers (**B**). Median pRNFL (**C**) and total macular volume (TMV) (**D**) were reduced in *TREX1* mutation carriers. G, global; GCL, ganglion cell layer; I, inferior; ILM, inner limiting membrane; INL, inner nuclear layer; IPL, inner plexiform layer; N, nasal; ONL, outer nuclear layer; OPL, outer plexiform layer; RNFL, retinal nerve fiber layer; RPE, retinal pigment epithelium; S, superior; T, temporal.

RESULTS

Patients and Controls

We included 34 eyes of 17 *TREX1* MC and 18 eyes of 9 controls. MC and controls did not differ in age (median age [IQR] 54 [45–62] vs 58 years [54–65], $P = 0.11$) or sex (65 vs 56% female, $P = 0.69$). Retinopathy was observed in 22 eyes (from 12 patients with RVCL-S), and no controls showed signs of retinopathy. Fourteen eyes of RVCL-S patients had undergone previous photocoagulation treatment, 3 in a scanned region. Five eyes were affected by secondary glaucoma. Median IOP [IQR] in patients with RVCL-S was 14 mm Hg [13–16]. Median visual acuity [IQR] in patients with RVCL-S was 0.0 logarithm of the minimum angle of resolution [0.0–0.2].

Mean Peripapillary Retinal Nerve Fiber Layer and Total Macular Volume

The pRNFL was significantly thinner in *TREX1* MC compared with that in controls (median [IQR] 76 [60–99] vs 99 [87–108] µm, $P < 0.001$) (Fig. 1C). Furthermore, all sectors, with exception of the temporal sector, showed significant thinning in *TREX1* MC (Fig. 1A, Table 1). TMV was decreased in *TREX1* MC compared with that in controls (median [IQR] 8.1 [7.4–8.5] vs 8.7 [8.4–8.8] mm^3, $P = 0.006$) (Fig. 1D). After exclusion of eyes affected by secondary glaucoma and photocoagulation treatment in scanned regions, pRNFL (median [IQR] 78 [62–99] vs 99 [87–108], $P = 0.003$) and TMV (median [IQR] 8.2 [7.5–8.5] vs. 8.7 [8.4–8.8], $P = 0.029$) remained thinner. We demonstrated that decreased pRNFL thickness and reduction of TMV already occurs as early as age 42 (Fig. 2).

Inner Retinal Layers

Decrease in TMT and individual retina layers thickness was demonstrated for the ganglion cell layer and inner plexiform layer (Table 2). The ganglion cell layer showed the most striking reductions. Although most patients demonstrated patchy thinning of the ganglion cell layer (GCL), 4 patients demonstrated sectorial thinning. Three of these patients had no overt signs of retinopathy at the time of scanning.

Spectral Domain Optical Coherence Tomography Measurements as Early Biomarkers for Retinal Vasculopathy With Cerebral Leukoencephalopathy and Systemic Manifestations

Importantly, in 9 of 12 eyes in which funduscopic examination did not detect signs of retinopathy, decreased pRNFL thickness or reduction of TMV could already be detected.

TABLE 1. Thickness of peripapillary sectors in *TREX1* mutation carriers

	TREX1 MC, Median (IQR), μm (n = 33*)	Controls, Median (IQR), μm (n = 18)	Estimate	CI	*P*
Nasal sup.	82 (63–97)	102 (90–114)	−23.3	−42.0 to −4.7	0.014†
Nasal	58 (45–78)	79 (68–104)	−26.5	−42.8 to −10.1	0.002‡
Nasal inf.	79 (60–109)	124 (90–143)	−34.4	−56.6 to −12.2	0.002†
Temporal inf.	102 (64–131)	135 (120–144)	−32.6	−52.7 to −12.5	0.001‡
Temporal	59 (51–73)	62 (57–70)	−1.5	−12.5 to 9.5	0.79
Temporal sup.	108 (77–130)	131 (123–143)	−21.6	−39.1 to −4.1	0.016†

*In one patient, measurements of one eye were not possible because of the patient's inability to focus.
†$P < 0.05$
‡$P < 0.01$.
CI, confidence interval; IQR, interquartile range; MC, mutation carriers.

DISCUSSION

We demonstrated decreased pRNFL thickness and reduction of TMV in patients with RVCL-S. The pRNFL contains unmyelinated axons of ganglion cells found in the ganglion cell layer, thus showing loss of intraocular axonal integrity in RVCL-S. In addition, we found a thinning of the inner plexiform layer, where dendrites from inner nuclear layer neurons are located. Our study findings also indicate an effect of RVCL-S on retinal neurons. Thus, indicating that OCT findings might provide useful biomarkers, as well as pathophysiological insights in the mechanism of RVCL-S and possibly other vasculopathies.

As very little is known about OCT findings in RVCL-S, we chose one primary outcome focusing on one overall measurement of the peripapillary region (pRNFL thickness) while the other focused on the macular region (TMV). We deliberately did not choose the GCL as a primary outcome because we were not only interested in macular thinning due to neuronal loss. As TMV is frequently used in the literature with similar conditions,

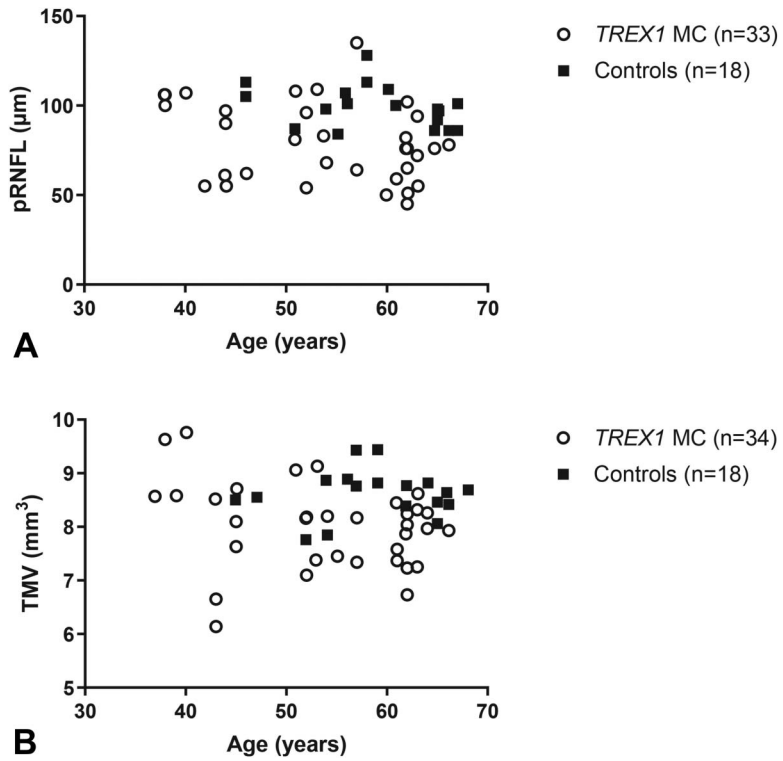

FIG. 2. Distribution of peripapillary retinal nerve fiber layer thickness (**A**) and total macular volume (**B**) with age in *TREX1* mutation carriers and controls. MC, mutation carriers; pRNFL, peripapillary retinal nerve fiber layer; TMV, total macular volume.

TABLE 2. Thickness of macula layers in *TREX1* mutation carriers

	TREX1 MC, Median (IQR), μm (n = 34)	Controls, Median (IQR), μm (n = 18)	Estimate	CI	*P*
Total macular thickness	296 (267–314)	316 (308–323)	−21.8	−38.1 to −5.6	0.009*
Macular RNFL	23 (20–27)	26 (24–27)	−2.7	−5.6 to 0.2	0.07
Ganglion cell layer	30 (22–37)	39 (36–41)	−8.7	−13.2 to −4.2	<0.001†
Inner plexiform layer	27 (24–34)	34 (31–35)	−5.1	−8.1 to −2.2	0.001*
Inner nuclear layer	35 (30–38)	35 (34–39)	−1.8	−4.8 to 1.3	0.25
Outer plexiform layer	29 (26–31)	29 (28–30)	−0.3	−1.8 to 1.2	0.70
Outer nuclear layer	69 (65–74)	70 (63–74)	−0.2	−6.3 to 6.0	0.96
Retinal pigment epithelium	14 (13–15)	14 (13–15)	−0.2	−1.2 to 0.8	0.68

*$P < 0.01$.
†$P < 0.001$.
CI, confidence interval; IQR, interquartile range; MC, mutation carriers; RNFL, retinal nerve fiber layer.

we chose this outcome to more easily compare the results across diseases (13). As TMT and TMV are highly correlated, we included TMT as a secondary outcome.

As RVCL-S is both a retinal vasculopathy and a neurodegenerative disorder, it is difficult to determine whether GCL loss is due to retinal disease or retrograde transsynaptic degeneration. The display of a patchy pattern of GCL loss in most patients is most consistent with retinal disease. Nonetheless, GCL loss is already apparent without overt retinal disease and that this can also occur in a sectorial pattern may suggest that retrograde transsynaptic degeneration could also play a role. Our findings may suggest that retrograde trans-synaptic degeneration occurs (and might be objectifiable in early disease stages), but also that retinal damage may be the main reason for further GCL thinning when retinopathy becomes more apparent. Studying (pre) symptomatic patients over time and relating OCT findings to MRI markers will help further elucidate these mechanisms for retinal loss.

There have been inconsistent reports on whether neurodegeneration of the retina occurs in diabetes mellitus. It seems that individual patient characteristics (e.g., diabetes type, control of disease, and duration) might favor neurodegeneration. Nonetheless, several studies found thinning of the pRNFL and GCL (14). Moreover, in early stages of diabetes before retinal vascular damage manifests, OCT findings have suggested that retinal neurodegeneration already occurs (7). Patients with hypertensive retinopathy also have lower central macular thickness and pRNFL thickness compared with controls (15). Interestingly, patients with end-organ damage had significantly lower SD-OCT measurements, indicating its use as a diagnostic biomarker. Vascular retinopathy seen in RVCL-S is similar to diabetic and hypertensive retinopathy. We now demonstrate that the findings on optical coherence tomography are also similar.

Moreover, pRNFL thinning has also been reported in other hereditary cerebral angiopathies, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Dutch-type hereditary (D-) cerebral amyloid angiopathy (CAA) (13,16). In these disorders, macula thinning was not found. However, in other disorders with multisystemic inflammatory involvement, such as Behçet disease, an inflammatory multisystemic chronic vasculitis, and systemic lupus erythematosus decreased macular and RNFL thickness was demonstrated (17,18). OCT findings are also promising biomarkers for neurodegenerative disorders, such as Alzheimer's disease. In patients with Alzheimer's disease, a reduction of macular volume correlated with cognitive impairment, and in a population-based study, thinner pRNFL was associated with an increased risk of developing dementia (8,9). In addition, macular and ganglion cell complex thickness were found to associate with the presence of dementia (19). Taken together, this indicates a promising role for retinal thickness as a diagnostic and prognostic biomarker not only for rare but also for common neurovascular disorders of the eye and brain.

This exploratory study may have some limitations. First, invasive fluorescein angiography was not performed because we focused on noninvasive techniques. Therefore, we cannot report on, for instance, capillary drop out and the size of foveal avascular zone, while this would have been interesting. However, fluorescein angiography is a procedure with possible side effects that only depicts the current vascular status at time of investigation and does not allow for evaluation of retinal tissue. OCT, in contrast, captures the permanent scar-like tissue damage, which is still present even in inactive disease stages. Nonetheless, in further studies, it may still be useful to systematically evaluate findings on fluorescein angiography and to compare these to noninvasive tools such as OCT techniques. Second, we cannot fully exclude an influence of photocoagulation treatment on OCT measurements. As patients with more severe retinal vasculopathy are more likely to receive photocoagulation treatment, the distinction of causality for retinal thinning may be difficult. However, most of our patients who received laser photocoagulation treatment were treated only in the periphery, and for our

secondary analyses, only eyes for which the regions of interest were not treated by photocoagulation were selected, thus theoretically decreasing the effect of treatment on our findings. Our findings are further supported by what has been shown in diabetic retinopathy. Laser treatment is used less frequently and thinning of the pRNFL on OCT has still been demonstrated, even before other signs of diabetic retinopathy appear (20,21). A third limitation of our study is the relatively small sample size because of the rarity of the disorder that also led to limited availability of individuals younger than 50 years. As such, currently no definite conclusion can be formulated about using SD-OCT findings as very early biomarkers from our exploratory study. Moreover, our study might have been underpowered for subtle retinal changes. Nonetheless, patients in their forties already have retinal thinning while funduscopic examination detected no signs of retinopathy. Finally, as is justified by the exploratory nature of our study, the significance level was kept at 0.05, although multiple statistical tests were performed. We did perform adjustment for intereye correlation. A major strength of our study is the use of a unique hereditary neurovascular model for retinopathy and vascular dementia in which different disease stages can be studied in mutation carriers.

Currently, the retinopathy seen in RVCL-S is classified based on results of funduscopy (and if indicated, fluorescein angiography) (3,22). Almost all eyes without signs of retinopathy had already demonstrated retinal thinning highlighting the need to update retinopathy criteria with the use of new ophthalmological techniques such as OCT in general and specifically for RVCL-S.

It is vital for patients with RVCL-S that they are recognized by ophthalmologists. Not only is ophthalmological monitoring critical but also neurological monitoring and treatment for anemia, hypertension, and kidney failure might be necessary. If the diagnosis is not recognized, this can lead to unnecessary, possibly harmful, biopsies (including, but not limited to, brain and kidney biopsies). Furthermore, misdiagnosis can have severe treatment implications. The diagnosis of RVCL-S should be suspected in adult patients of middle age presenting with vascular retinopathy and/or focal or global neurologic deficits, particularly in the setting of a positive family history of retinopathy or neurological diseases (2,6,23). Given that patients often present with vision loss, the ophthalmologist should be cautious in cases of vascular retinopathy without an apparent etiology. Of note, a negative family history does not exclude RVCL-S because de novo pathogenic variants can occur (24). Furthermore, family members with RVCL-S may be misdiagnosed with other conditions (e.g., neurodegenerative disorders, vascular dementia, brain tumor, multiple sclerosis, hypertensive retinopathy, and diabetic retinopathy).

This study demonstrated retinal thinning in patients with RVCL-S in the peripapillary and macular area, even when funduscopic examination was normal. As OCT is a safe, noninvasive, and precise diagnostic tool, we expect an increasing impact of OCT on the future diagnostic workup of patients with RVCL-S. Moreover, SD-OCT measurements may be used as a preclinical biomarker not only in RVCL-S but also in common neurovascular conditions such as diabetic retinopathy and vascular dementia, for which RVCL-S serves as a monogenic model.

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