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Visual electrophysiological responses in subjects with cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

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Abstract

Objectives: To evaluate visual electrophysiological responses in subjects with cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Methods: Three subjects (one male and two females, mean age 55.3 ± 2.9 years) belonging to an Italian family already diagnosed with CADASIL through clinicopathological and genetic studies and 14 control subjects (6 males and 8 females, mean age 52.7 ± 3.6 years) were enrolled in the study. Flash electroretinogram (ERG), oscillatory potentials (OPs) and simultaneous recordings of pattern electroretinogram (PERG) and visual evoked potentials (VEPs) were assessed in all 3 subjects with CADASIL and age-matched controls.

Results: Subjects with CADASIL showed: reduced ERG, OP and PERG (N35-P50, P50-N95) amplitudes with respect to our normal limits; delayed PERG (N35, P50) and VEP (P100) implicit times when compared with our normal limits; and VEP (N75-P100) amplitudes and retinocortical times within our normal limits.

Conclusions: Subjects with CADASIL present a dysfunction in the outer, middle and innermost retinal layers when the index of neural conduction in the postretinal visual pathways is normal. The delay in visual cortical responses observed in subjects with CADASIL may be ascribable to retinal impairment with a possible functional sparing of the postretinal visual structures.

Keywords: Electroretinogram; Visual evoked potential; CADASIL; Visual pathways; Leukoencephalopathy; Smooth muscle cell; Cerebral arteriopathy

1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a small- and medium-sized artery disease associated with missense point mutations of the Notch3 gene on chromosome 19 (Tournier-Lasserve et al., 1993; Clair et al., 1995; Joutel et al., 1996). The clinical picture of this disease is characterized by headaches, transient ischemic attacks, recurrent strokes with onset during mid-adulthood, and progression leading to dementia with pseudobulbar palsy (Chabriat et al., 1995). Neuropathological studies indicate that the principle lesion consists of a marked thickening of the media of the small- and medium-sized cerebral arteries, with deposition of granular material and damage to the smooth muscle cells (SMCs) (Davous and Fallet-Bianco, 1991; Baudrimont et al., 1993; Gray et al., 1994; Rouchoux et al., 1995; Malandrini et al., 1996). Similar changes have been observed in other areas, particularly in muscle and skin arteries (Zhang et al., 1994; Rouchoux et al., 1995; Schröder et al., 1995; Ebke et al., 1997; Goebel et al., 1997; Schultz et al., 1999). Histologically, a widespread myelin pallor and multiple small infarcts in the white matter and basal ganglia

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may be observed (Davous, 1998; Filley et al., 1999). However, the relationship between these pathological findings and the genetic lesions remains unknown, as do the exact determinants of the clinical progression of this disease.

Several studies performed using visual evoked potentials (VEPs) have revealed a delay in neural conduction in the visual pathways in demyelinating diseases (Celesia et al., 1986; Narayanan et al., 1997; Parisi et al., 1997, 1999a,b; Trapp et al., 1999). These electrophysiological data led us to believe that a similar impairment may occur in subjects with CADASIL.

VEPs are defined as variations of bioelectrical potentials in the occipital cortex evoked by visual stimuli (Celesia et al., 1986). They express complex neurosensorial events linked to the transduction and transmission of neural impulses along visual pathways, from the retinal photoreceptors to the occipital cortex. Therefore, in the presence of an abnormal VEP response, a functional evaluation of the retinal structures is required to verify whether this impairment depends exclusively on a delay in neural conduction in the visual pathways or is associated with retinal dysfunction.

Particular electrophysiological methods allow us to explore and dissect different structures contributing to retinal function. The flash electroretinogram (ERG) reflects the bioelectric activity of the outer retinal layers (Armington, 1974), oscillatory potentials (OPs) are more often generated in the middle retina (Algvere, 1968; Ogden, 1973; Wachtmeister and Dowling, 1978; Heynen et al., 1985), while the electroretinographic signal evoked by patterned stimuli (PERG) is related to the bioelectric activity of the innermost retinal layers (Maffei and Fiorentini, 1981, 1982; Hollander et al., 1984; Maffei et al., 1985; Morrone et al., 1994; Parisi et al., 1999a,b).

The aim of this study was, therefore, to evaluate retinal function and neural conduction in the visual pathways by using ERG, OP, PERG and VEP recordings in subjects with full-blown CADASIL syndrome (Malandrini et al., 1996).

2. Subjects and methods

2.1. Subjects

Three subjects belonging to an Italian family already diagnosed with CADASIL (one male and two females, mean age 55.3 ± 2.9 years) and 14 control subjects (6 males and 8 females, mean age 52.7 ± 3.6 years) were enrolled in this study. The inclusion criteria for CADASIL subjects were: normal intraocular pressure (<21 mmHg), normal visual acuity (10/10), and no ocular or metabolic problems.

The inclusion criteria for the control subjects were: normal intraocular pressure (<21 mmHg), normal visual acuity (10/10), normal visual field (Goldmann perimetry or Humphrey 24.2) and no ocular, metabolic or neurological problems.

The diagnosis of CADASIL was based on clinical and genetic studies (Malandrini et al., 1996). Extensive laboratory investigations failed to demonstrate any known risk factor for vascular disease.

Informed consent was received from all participants in the study. The research followed the tenets of the Declaration of Helsinki.

2.1.1. Subject #1 (male 52 years)

The onset of clinical symptoms appeared at 37 years of age, when the subject first experienced right facial paresthesia and headache, both of which regressed spontaneously within a few days. Two similar clinical episodes reoccurred at 41 and 43 years of age. Visual acuity in his right eye was absent for traumatic reasons. Brain magnetic resonance imaging (MRI) showed numerous bilateral, almost symmetrical, areas of T2-weighted hyperintensity in the white matter that tended to coalesce.

2.1.2. Subject #2 (female 62 years)

At 15 years of age this subject had a sudden episode of headaches, visual impairment, speech difficulty, weakness and paresthesia in the upper right limb, but recovered completely in 48 h. She continued to have similar, but less severe, episodes two or three times a year. At the age of 44 years, she was hospitalized with a new attack characterized by intense headaches, aphasia and disorientation. The following year she had a similar clinical episode. Brain MRI showed confluent, bilateral, symmetrical areas of hyperintensity in the cerebral white matter.

2.1.3. Subject #3 (female 58 years)

This subject did not have episodes of acute neurological symptoms but only occasional headaches and amnesia. After an isolated intense headache attack at 52 years of age, during which the subject exhibited temporary spatial and temporal disorientation, a brain MRI was performed. This showed diffuse, bilateral T2-weighted hyperintensity, which was more accentuated in the frontotemporal region, in the cerebral white matter.

2.2. Laboratory tests

Routine blood analysis, electrocardiogram, echocardiogram, Doppler sonography of the carotid and vertebrobasilar arteries were normal in all 3 CADASIL subjects. No subject had hypertension and, more importantly, a history of other risk factors for cerebrovascular disease.

2.3. Methods

According to our previously published studies (Uccioli et al., 1995; Parisi et al., 1997, 1998a,b, 1999a,b), the following electrophysiological evaluations were performed.

2.3.1. Flash ERG

ERGs were recorded according to standard ISCEV (Marmor and Zrenner, 1998). Prior to the experiment, each subject was adapted to the dark for 20 min. The pupils were maximally dilated (tropicamide 1%).

The bioelectric signal was recorded by means of platinum hook electrodes inserted into the external corner of the inferior eyelid (active electrode). Local anesthesia was provided by application of novesine 0.4%. A silver–silver chloride electrode was positioned and fixed with collodion near each orbital rim temporally as a reference electrode for the corresponding eye. A silver–silver chloride electrode was positioned and fixed with collodion in Fpz (International 10–20 System of EEG recording) (ground electrode). The interelectrode resistance was lower than 5 kΩ.

2.3.2. ERG (maximal combined response) recordings

The visual stimulus was a BM 6000 Ganzfeld (Biomedica Mangoni, Pisa, Italy) at 0.1 J of intensity (1.8 cd-s-m^2) with a duration of 5 ms, presented at the temporal frequency of 0.1 Hz.

The signal was amplified (gain 5000), filtered (bandpass 1–100 Hz) and averaged with automatic rejection of artifacts (40 events for every trial) by BM 6000. The analysis time was 125 ms. The typical ERG is a biphasic signal characterized by a certain number of waves, two of which (a- and b-waves) have a mean latency of 16 and 40 ms in normal subjects.

2.3.3. Oscillatory potentials (OPs)

The visual stimulus was BM 6000 Ganzfeld at 1 J (18 cd-s-m^2) of intensity, with a duration of 3 ms presented 15 s apart to the dark-adapted eyes. The signal was amplified (gain 5000) and filtered (bandpass 100–5000 Hz). The averaging process (including the second and subsequent responses) was performed with automatic rejection of artifacts by BM 6000 (20 events for every trial). The analysis time was 125 ms. OPs are characterized by a number of waves: OP1, OP2, OP3, OP4. We considered OP amplitude as the summation of the OP1 + OP2 + OP3 + OP4 amplitudes.

2.3.4. Simultaneous recordings of PERG and VEP

The subjects under examination were seated in a semi-dark, acoustically isolated room in front of the display surrounded by a uniform field of luminance of 5 cd/m^2. Prior to the experiment, each subject was adapted to the ambient room light for 10 min to obtain a pupil diameter of about 5 mm. Mydriatic or miotic drugs were never used. Stimulation was monocular after occlusion of the other eye. Visual stimuli consisted of checkerboard patterns (contrast 80%, mean luminance 110 cd/m^2) generated on a TV monitor and reversed in contrast at a rate of two reversals per second. At the viewing distance of 114 cm, the check edges subtended 15 min of visual angle. The monitor subtended 18° and a small red target (0.5°) was placed in the center of the stimulus field to maintain stable fixation. The refraction of all subjects was corrected according to the viewing distance.

2.3.4.1. PERG recordings. The bioelectric signal was recorded by a small Ag/AgCl skin electrode placed over the lower eyelid. PERGs were derived bipolarly between the stimulated (active electrode) and the patched (reference electrode) eye using the method previously described (Fiorentini et al., 1981). The ground electrode was in Fpz. The interelectrode resistance was lower than 3 kΩ. The signal was amplified (gain 50 000), filtered (bandpass 1–30 Hz) and averaged with automatic rejection of artifacts (200 artifact-free events were averaged for every trial) by BM 6000. The analysis time was 250 ms. The transient PERG response is characterized by a number of waves with 3 successive peaks of negative, positive and negative polarity. In normal subjects, these peaks have the following implicit times: 35, 50 and 95 ms (N35, P50, N95).

2.3.4.2. VEP recordings. The bioelectric signal was recorded using Ag/AgCl cup-shaped electrodes fixed with collodion in the following positions: active electrode at Oz, reference electrode at Fpz; ground on the left arm. The interelectrode resistance was kept below 3 kΩ. The bioelectric signal was amplified (gain 20 000), filtered (bandpass 1–100 Hz) and averaged (200 artifact-free events were averaged for every trial) by BM 6000. The analysis time was 250 ms. The transient VEP response is characterized by a number of waves with 3 successive peaks of negative, positive and negative polarity. In normal subjects, these peaks have the following implicit times: 75, 100 and 145 ms (N75, P100, N145).

We accepted VEP and PERG signals with a signal-to-noise ratio of >2. The noise was measured by recording the bioelectric signals (200 averaged events), while the monitor was screened by cardboard; a retinal noise (peak-to-peak measure) of <0.1 μV (mean 0.086 μV) was observed in all subjects tested. For all VEP and PERG recordings, the implicit time and the peak-to peak amplitude of each of the averaged waves were measured directly on the displayed records by means of a pair of cursors.

Simultaneous VEP and PERG recordings allow us to derive an index of neural conduction in the postretinal visual pathways, expressed as the difference between VEP P100 implicit time and PERG P50 implicit time. This index was called retinocortical time (RCT) by Celesia et al. (1986).

3. Results

The main clinical and electrophysiological data related to the CADASIL subjects are shown in Tables 1 and 2.

3.1. ERG and OPs

ERG and OP recordings are shown in Fig. 1. In all 3

Table 1
Clinical and electrophysiological findings in subjects with CADASIL and mean data ± 1 SD observed in control subjects[a]

Subjects	Sex	Age (years)	Eye	VA	IOP	Flash electroretinogram (ERG)				
						a-wave implicit time (ms)	b-wave implicit time (ms)	a-wave amplitude (μV)	b-wave amplitude (μV)	OPs amplitude (μV)
CADASIL #1	F	57	RE	10/10	16	16.2	37.8	26.9*	75.8*	67.6*
			LE	10/10	14	16.4	38.7	14.8*	63.9*	68.3*
CADASIL #2	F	57	RE	10/10	16	15.6	35.6	7.8*	37.6*	25.3*
			LE	10/10	16	15.6	36.6	9.9*	43.3*	26.4*
CADASIL #3	M	52	LE	10/10	15	16.6	41.4	16.9*	75.5*	66.6*
Controls ($N = 14$) (mean ± 1 SD)	6M/8F	52.7 ± 3.6	–	10/10	14 ± 2	15.2 ± 1.60	33.8 ± 3.10	43.4 ± 4.3	122.3 ± 10.7	111.3 ± 6.26

[a] RE, right eye; LE, left eye; VA, best corrected visual acuity; OPs, oscillatory potentials, addition of OP1 + OP2 + OP3 + OP4 amplitudes. In subject #3 the RE was not considered because it was affected by anisometric ambliopia. *, abnormal when compared with our normal limits.

CADASIL subjects (#1, #2 and #3), the a- and b-wave implicit times were within our normal limits (expressed as mean values + 3 SD of controls: 20.0 and 43.1 ms, respectively), while the a-wave, b-wave and OP amplitudes were lower than our normal limits (expressed as mean values − 3 SD of controls: 30.5, 90.2 and 92.5 μV, respectively).

3.2. PERG and VEP

Simultaneous recordings of VEP and PERG are shown in Fig. 2. In all 3 CADASIL subjects (#1, #2 and #3) the PERG N35 and P50 implicit times were longer than our upper limits (expressed as mean values + 3 SD of controls: 37.5 and 56.6 ms, respectively) and the PERG N35-P50 and P50-N95 amplitudes were lower than our normal limits (expressed as mean values − 2 SD of controls: 1.03 and 1.50 μV, respectively).

The CADASIL subjects (#1, #2 and #3) showed delayed VEP P100 implicit times when compared with our upper limit (expressed as mean values + 3 SD of controls: 112.68 ms), while the VEP N75-P100 amplitudes were within our normal limits (expressed as mean values − 1 SD of controls: 5.33 μV). Retinocortical times were within our normal limits (expressed as mean values + 3 SD of controls: 58.36 ms).

4. Discussion

In CADASIL subjects with the full-blown syndrome, we observed an impairment in retinal bioelectrical responses as assessed by ERG, OP and PERG recordings.

ERG represents the response of the entire retinal activity and the sensorial mechanism related to the transduction of the light stimulus to a bioelectric impulse. It is characterized by different waves which reflect the activity of different retinal structures: the a-wave reflects extracellular currents in the photoreceptor layer generated by light absorption in the outer segments, while the b-wave is considered to arise from transmembrane potential changes in the Müller and bipolar cells (Berninger and Arden, 1991). The OPs are small amplitude, high frequency waves superimposed upon the ascending portion of the b-wave (Van der Torren et al., 1988; Lachapelle, 1991). Their origin is not well defined but likely to be related to different subpopulations of amacrine cells (Heynen et al., 1985).

The impaired ERG and OP responses suggest that a dysfunction in the outer and middle retinal layers occurred in our CADASIL subjects, even in the absence of functional (all the patients had a visual acuity of 10/10) or clinical (none of these subjects showed ophthalmoscopic or fluorescein angiographic signs of retinopathy) visual symptoms. Since OPs are considered the electrophysiological indica-

Table 2
Simultaneous recordings of visual evoked potentials and pattern electroretinogram[a]

	PERG N35 implicit time (ms)	PERG P50 implicit time (ms)	PERG N35-P50 amplitude (μV)	PERG P50-N95 amplitude (μV)	VEP P100 implicit time (ms)	VEP N75-P100 amplitude (μV)	RCT (ms)
CADASIL #1	41.3*	60.6*	0.7*	1.1*	115*	7.0	54.4
	42.3*	60.3*	0.4*	1.1*	114*	8.4	53.7
CADASIL #2	42.5*	64.8*	0.4*	0.9*	115*	7.0	50.2
	38.4*	63.4*	0.5*	1.0*	114*	8.1	50.6
CADASIL #3	39.4*	63.6*	0.7*	1.1*	114*	6.1	50.4
Controls ($N = 14$)	32.3 ± 1.75	51.2 ± 1.80	1.41 ± 0.19	1.86 ± 0.18	104.07 ± 2.87	6.98 ± 1.65	52.96 ± 1.80

[a] RCT, retinocortical time: difference between VEP P100 and PERG P50 implicit times. *, abnormal when compared with our normal limits.

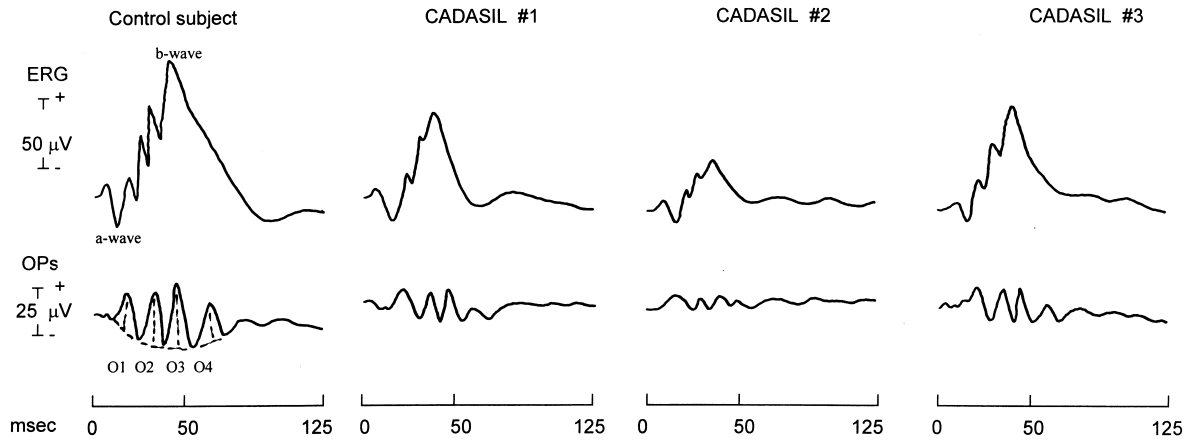

Fig. 1. ERG and OP recordings in one control subject and in subjects with CADASIL. Subjects #1, #2 and #3 present a reduction in ERG a- and b-wave and OP amplitudes.

tors of retinal ischemia caused by reduced circulation in the retinal blood vessels (Speros and Price, 1982), this impairment could be ascribed to a vascular involvement that affects the retinal vessels similar to those that affect brain arteries (Davous and Fallet-Bianco, 1991; Baudrimont et al., 1993; Gray et al., 1994; Rouchoux et al., 1995; Malandrini et al., 1996). This vascular hypothesis is supported by data obtained in diabetic patients (without fluorescein angiographic signs of retinopathy), in whom similar electroretinographic responses (reduction in OP and b-wave amplitudes) have been observed (Parisi et al., 1997).

We observed PERG responses with delayed implicit times and reduced amplitudes in all 3 CADASIL subjects. PERG is known to reflect the bioelectric activity of the innermost retinal layers (ganglion cells and their fibers), as demonstrated in studies by Maffei and Fiorentini (1981, 1982) that show ganglion cell fiber retrograde degeneration after section of the optic nerve in cats and monkeys. This phenomenon is related to a reduction, and eventual disappearance, of the PERG response (Maffei and Fiorentini, 1981, 1982; Hollander et al., 1984; Maffei et al., 1985). Despite a significant amount of information collected from different animal species, data from human eyes are still controversial (Odom et al., 1983). However, recent studies performed on subjects with multiple sclerosis or ocular hypertension (Parisi et al., 1999a,b), in whom a relationship between PERG responses and the retinal nerve fiber thickness has been observed (evaluated in vivo by optical coherence tomography-OCT), have suggested that the integrity of ganglion cell fibers is essential for the generation of a normal PERG response in humans as well.

Our PERG results suggest a dysfunction in the innermost retinal layers in CADASIL subjects. Nevertheless, the presence of a concomitant impairment in the outer retinal layers (reduced ERG and OPs responses) leads us to believe that the involvement of the luminance sensitive retinal generators (preganglionic cells) cannot entirely be excluded in the abnormal PERG responses we observed.

We observed a delay in VEP P100 implicit time and normal VEP N75-P100 amplitudes in all 3 CADASIL subjects. This finding may represent electrophysiological evidence of a delay in cortical responses to visual stimuli. There are no reports of electrophysiological studies on evoked potentials in CADASIL in the literature and few

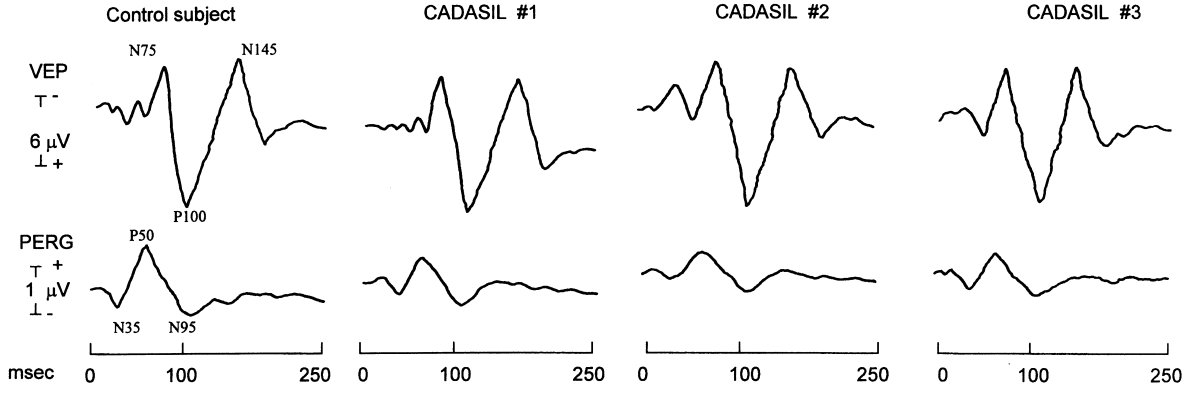

Fig. 2. Simultaneous recordings of VEP and PERG in one control subject and in subjects with CADASIL. Subjects #1, #2 and #3 present a delay in PERG N35 and P50 implicit times and in VEP P100 implicit times. Reduced PERG amplitudes and normal VEP amplitudes were observed.

studies on electrophysiological responses in leukoaraiosis. Somatosensory evoked potentials (SEPs) have been used to demonstrate that central conduction time is longer when white matter attenuation is more extensive (Abbruzzese et al., 1984; Kato et al., 1990), a finding which suggests a possible impairment of axonal conduction in this site.

Consequently, a demyelinating factor may be a possible explanation for our VEP results. This hypothesis is supported by a recent study (Chabriat et al., 1999) performed in vivo with diffusion tensor MRI (Jones et al., 1999) that showed major diffusion changes in the white matter of subjects with CADASIL, particularly in the extracellular space (Chenevert et al., 1990; Beaulieu and Allen, 1994; Ono et al., 1995; Jones et al., 1999).

In our CADASIL subjects we observed PERG responses associated with normal RCT. RCT, which represents an electrophysiological index of neural conduction in the postretinal visual pathways (Parisi et al., 1998a), is known to be delayed in demyelinating diseases (Celesia et al., 1986). Since VEP responses derive from retinal bioelectrical activity (ERG, OPs and PERG responses) together with neural conduction in the postretinal visual pathways (evaluated by the RCT index), our ERG, OP and PERG results lead us to believe that the abnormal visual cortical responses we observed may be ascribable to a retinal dysfunction, with a functional sparing of the postretinal neural conduction. It is therefore likely that the aforementioned demyelinating process (Chabriat et al., 1999) does not play an important role in the postretinal neural conduction in the subjects we assessed or at the stage of disease in which they were.

In conclusion, our results suggest that subjects with CADASIL present a dysfunction in the outer, middle and innermost retinal layers, even when the index of neural conduction in the postretinal visual pathways is normal. Therefore, the delay in visual cortical responses observed in subjects with CADASIL may be ascribable to a retinal impairment with a possible functional sparing of the postretinal visual structures.

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