Chapter 7
Optical Coherence Tomography in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is a neurodegenerative disorder, which is likely to start as mild cognitive impairment (MCI) several years before its full-blown clinical manifestation. In the last two decades, optical coherence tomography (OCT) has been used to observe a significant loss in peripapillary retinal nerve fiber layer (RNFL) and in macular thickness and volume in patients affected by a form of mild to severe dementia. These morphological abnormalities correlate to some extent with the severity of the disease as evaluated with neuropsychological tests. Furthermore, these structural measures correlate with electrophysiological parameters of pattern electroretinogram, reflecting integrity of the innermost retinal layers, but not with those of the visual evoked potentials, reflecting activity of the post-chiasmatic visual pathway. The latter evidence suggests that RNFL thickness reduction is related to neuronal degeneration in the ganglion cell layer and not to a retrograde degeneration from the post-chiasmatic visual pathway. These data suggest a possible role of OCT in monitoring the progression of AD and in assessing the effectiveness of purported AD treatments.

Keywords Alzheimer's disease • Optical coherence tomography • Mild cognitive impairment • Electroretinogram • Psychometric testing • Retina

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Abbreviations

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale
aMCI	Amnestic type of mild cognitive impairment
APP	Beta-amyloid precursor protein
ERG	Electroretinogram
GCL	Ganglion cell layer
HRT	Heidelberg retina tomograph
OCT	Optical coherence tomography
ON	Optic nerve
PERG	Pattern electroretinogram
PS1	Presenilin 1
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RNFL	Retina nerve fiber layer
VEP	Visual evoked potential

7.1 Introduction

Alzheimer's disease (AD) is the most common cause of dementia with an incidence that increases with age exponentially. According to the World Health Organization the worldwide prevalence of Alzheimer' disease (AD) is increasing yearly and receives growing attention not only because it affects quality of life, and also because has a significant economic impact, being a major public-health problem [1]. The recent publication of the Global Burden of Disease survey 2012 shows that among neurological conditions, AD is the third highest cause of disability in the world [2].

AD is a brain degenerative disorder, where inherited susceptibility and environmental factors are probably interrelated [3, 4]. The clinical evolution of AD is a slowly progressive and episodic memory loss as the predominant symptom, with various accompanying signs including aphasia, apraxia, and agnosia, and general cognitive symptomology, such as impaired judgement, decision-making, and orientation [3]. Because of the slowness of the disease's progression, the neurodegenerative processes are likely to start 20–30 years before the clinical manifestation of AD. This transitional phase is recognized as mild cognitive impairment (MCI), which has memory deficit, preservation of general cognitive and functional abilities, and absence of diagnosed dementia as cardinal features [5]. The amnestic type of MCI (aMCI) shows the highest annual incidence conversion rate to AD [6].

Despite great advances in the understanding of AD pathophysiology in the last few years, the exact pathogenesis of AD and its precursor MCI is still not comprehensively understood.

At the histopathologic level, neuronal loss, beta-amyloid plaques, neurofibrillary tangles made of hyperphosphorylated tau and neuritic plaques, and granulovacuolar degeneration characterize the brain of AD [3]. These lesions have been seen in the

hippocampus and other limbic structures, as well as in the visual associative areas [7, 8], the primary visual cortex [9, 10], and in subcortical structures including the lateral geniculate nuclei and the superior colliculi [11–13], and within the retina [14, 15].

AD patients may be affected by various visual disturbances, such as deficit in contrast sensitivity [16–18], motion perception [19, 20], and color discrimination [21–23]. Historically, these visual dysfunctions in AD have been attributed to damage in primary visual cortex and to degenerative processes in primary and associative visual cortical areas, but cortical dysfunction alone cannot explain the pattern of observed defects. Multiple forms of evidence points toward the involvement of retinal ganglion cells and their axons in the optic nerve as a basis of the visual dysfunction in AD [14, 24].

In the last two decades, several studies have searched for the retinal involvement in AD pathophysiology. Sophisticated imaging techniques have been used, such as optical coherence tomography (OCT), scanning laser polarimetry, and pattern electroretinography (PERG), to assess the morphologic and functional changes of the retina in AD.

Optical Coherence Tomography (OCT) permits the objective quantification *in vivo* of the retinal nerve fiber layer (RNFL) that consists of axons that form the optic nerve and contributes partially to the retinal thickness. This method consists of a non-invasive technology allowing cross-sectional imaging of the eye [25, 26]. A relatively recent implementation of OCT, Spectral-Domain OCT, provides advantages in signal-to-noise ratio, permitting faster signal acquisition [27, 28]. Taking in mind that the human eye is an embryological protrusion of the brain, and the nerves and axons of the retinal nerve fiber layer (RNFL) are similar to those in the brain, it is not surprising that OCT has been widely employed in assessing RNFL thickness in several neuro-ophthalmological disorders [29–33].

The intent of this chapter is to provide a comprehensive overview of the results provided by the OCT technique as used to understand morphological retinal changes that occur due to the degenerative processes associated with Alzheimer's disease and other dementing disorders.

7.2 Retina and Alzheimer's Disease

As an integrated part of the nervous system, the retina is physiologically under senescence processes, the majority of them still under intense scrutiny. Therefore, in order to better evaluating AD patients, it is important to quantify the degree of thinning arising with age in the absence of pathological processes. It is also important to determine whether age-related loss is uniformly distributed across the optic disc or has any tendency to be sectorial, and might therefore be a confounding factor for a correct evaluation of disease-related processes.

In the quest for understanding the degenerative changes accompanying AD, researchers performed both histological and *in-vivo* studies on healthy subjects.

Using immunohistochemical techniques, Löffler and colleagues examined the presence and expression of amyloid-related proteins, the same that have been found in specimens of AD patients' brains, in the human retina collected from cadaver

eyes at various ages [15]. They did not find any abnormal deposits or immunoreactivity changes in the outer neural retina. On the other hand, they first proved the presence of tau proteins and amyloid precursor protein in the inner retina layers, including retinal ganglion cells and nerve fiber layer, of the human retina in older persons. Small amounts of beta-amyloid were detected in the sub-retinal pigment epithelium space [15].

The analysis of normal *in-vivo* human retinal nerve fiber layer thickness, as measured by time-domain OCT, has been repeatedly confirmed as an age-related reduction of RNFL thickness in normal subjects [34–37]. This thinning mainly involved the superior and inferior optic disc areas [38–40].

7.2.1 Animal Model of AD

One of the most recognised theories for the genesis of AD, the "amyloid cascade hypothesis", postulates that APP dysmetabolism and beta-amyloid deposition are the primary events that facilitate the disease process of AD [41].

In the past decade, through the use of genetic engineering techniques, transgenic (Tg) animal models over-expressing mutant forms of amyloid precursor protein (APP) and/or presenilin 1 (PS1) have been generated to mimic various aspects of AD pathology, including Aβ deposition, cognitive deficits, inflammation, and synaptic dysfunction, to test newly proposed therapeutic agents [42]. Recent publications have shown the accumulation of Aβ-plaques within the retina [43–46] and its microvasculature [47], retina ganglion cell death [48], and local neuroinflammation [47] in different Tg animal models. Nevertheless, these transgenic models only mimic part of the pathological features of AD.

An interesting and novel Tg AD rat model, TgF344-AD, expressing mutant human amyloid precursor protein (APPsw) and presenilin 1 genes, seems to more faithfully encapsulate all the features of AD. This animal model is characterized by an otherwise healthy long lifespan, but the rats suffer from later age cognitive decline, age-dependent cerebral amyloidosis, taupathy, gliosis, and frank neuronal loss that seems to parallel those in humans [49]. Recently, Tsai and colleagues investigated a group of TgF344-AD rats and age-matched wild type rats [50]. When compared with age-matched controls, the retinas of Tg rats demonstrated the presence of Aβ plaques, hypertrophic retinal pigment epithelial cells, signs of neuroinflammation, and a significant thinning of retinal choroid [50].

7.2.2 Histological Studies in Post-Mortem AD Eyes

In 1986, histological examination in a human post mortem study, revealed depletion of axons in the optic nerves from AD patients [14]. Sadun and colleagues were the first to demonstrate this primary AD-associated optic neuropathy and further, to characterize, by morphometric analysis, that the predominant effect was on the

largest retinal ganglion cells (M-cells) that contribute their large caliber fibers to the optic nerve [24]. Other studies [51, 52] failed to confirm the selective large axon losses. This discrepancy has been attributed, at least in part, to methodological biases such as a different *post-mortem* delays, different techniques in axonal counting and/or difficulties in obtaining well-preserved myelinated axons.

Extensive retinal ganglion cell loss in the central retina in AD was also observed in histological studies [14] or by other methods of evaluating the RNFL *in vitro*. Morphometric analysis of the central retina (fovea/foveola/parafoveal retina) in eyes from 9 AD and 11 age-matched controls revealing an overall decrease of 25 % in total numbers of neurons in the ganglion cell layer (GCL) (fovea/parafoveal retina) in AD as compared with control eyes [53]. Moreover, the most severe decrease was observed in the foveal region (–43 %) over the far temporal region. Similar results were obtained in AD patients with the evaluation of the peripheral retina: the neuronal loss was more pronounced in the superior and inferior quadrants (50–59 %) and a significantly increased ratio of astrocytes to neurons was detected when compared with control eyes [54]. Moreover, histological signs of degeneration in the retinal ganglion cells (RGCs) were described to include a vacuolated, "frothy" appearance of the cytoplasm in the absence of neurofibrillary tangles within the RGCs, or of neuritic plaques or amyloid angiopathy in the retinas or optic nerves in AD [55].

Koronyo-Hamaoui and colleagues recently identified retinal Aβ plaques in *post-mortem* eyes from 8 AD patients and in five suspected early stage cases, but not in five age-matched non-AD individuals [45].

Plaque-like structures were seen in two retinas from two AD patients, with thickening of retinal choroid and no changes in the retinal pigment epithelial cells [50]. Fibrillar tau or Aβ aggregates were seen in *post-mortem* retinas from the same AD patients that had been previously observed by using an *in-vivo* imaging technique [56].

7.2.3 Clinical Studies Based on the Subjective Evaluation of Fundus Photographs

The RNFL includes axons of ganglion cells, which form the origin of the optic nerve.

That retinal ganglion cell degeneration occurs in AD is further evident by means of the use of a boundary-tracking program and RNFL photographs. A higher proportion of AD patients showed signs of optic neuropathy manifesting as optic disc atrophy, pathologic optic disc cupping, and thinning of the neuroretinal rim and of the RNFL [57, 58]. Tsai et al. [57] observed an increased cup-to-disc ratio, cup volume, and decreased optic disc rim area in AD patients by optic nerve analyser.

Analyzing mild to moderate AD patients with RNFL fundus photographs, Lu and colleagues found that all the AD patients had different types of RNFL abnormalities, including diffuse and wedge shape nerve fiber layer drop-out [59]. These abnormalities in AD patients were associated with a higher cup–disc ratio of 39–43 % when compared to that in the control group.

However, it must be mentioned that these studies may have been biased by the subjective evaluation of fundus photographs.

7.3 *In-Vivo* Morphological Analysis in AD and MCI Patients

One confounding factor in analysing MCI and AD -related late-onset progressive changes is that there are anatomical and physiological changes normally found in aging eyes. In animal [60] and human [60, 61] studies a physiological age-dependent progressive loss of optic nerve fibers, with progressive decrease of mean axonal diameter has been demonstrated [62–64].

Optical coherence tomography (OCT) is a technique that can also be used in ophthalmology for the measurement of the macular thickness and volume. OCT can determine RNFL thickness of the peripapillary region reflecting axons and would allow quantification of axonal loss, measurement of macular thickness and volume would reflect retinal neurons, allowing quantification of neuronal loss [25].

Several previous studies using OCT techniques have examined the relationship between age and RNFL measurements. These have consistently shown that optic nerve, RNFL, and macular measurements with OCT all varied with age [36, 65], with the greatest decrease in mean RNFL occurring in the superior [39] and inferior quadrants [37], especially after age 50 years [38], and with the least decrease in the nasal and temporal quadrants [66, 67]. This age-related decline in normal RNFL measurements needs to be considered when considering or monitoring ocular disease.

However, as described below, the reduction in RNFL thickness observed in most studies on AD patients was significantly greater than that observed in the age-matched controls and thus cannot be exclusively ascribed to aging (see some illustrative OCT imaging in Fig. 7.1 and a synopsis of published OCT studies in AD and MCI in Table 7.1).

Parisi and colleagues were the first who used OCT to study a group of 17 AD patients affected from mild severity cognitive impairment and compared them with a group of 14 age-matched controls. In AD patients, OCT results showed thinning of the average peripapillary RNFL and in all quadrants examined, showing the involvement of the neuroretinal tissue in AD [68, 69].

The mean RNFL thickness was corroborated to be reduced in AD patients by several independent groups [59, 72, 77, 78], and even in patients affected with MCI [73]. Individual examination of the quadrants was even more revealing. Most studies observed a significant reduction of RNFL thickness in the superior quadrant [59, 70, 73, 74, 78], but for some also in the inferior quadrant [59, 73]. In contradistinction, the inferior quadrant seems more involved in MCI patients [73].

Some researchers studied optic nerves of AD patients by using confocal scanning laser ophthalmoscopy (cSLO). Ophthalmoscopy in combination with cSLO, revealed an enlargement in the mean vertical cup-to-disc ratio (clinician and instrument derived), rim volume, rim area, and reduced RNFL thickness in patients with AD with respect to controls [81]. Compared with individuals in the lowest quarter of values of cup-to-disc ratios, those with higher values generally had an increased risk of AD [81]. Lu et al. [59] also observed an enlarged cup-to-disc ratio and a thinner RNFL thickness in their 22 mild to moderate AD patients. In contrast, Kergoat

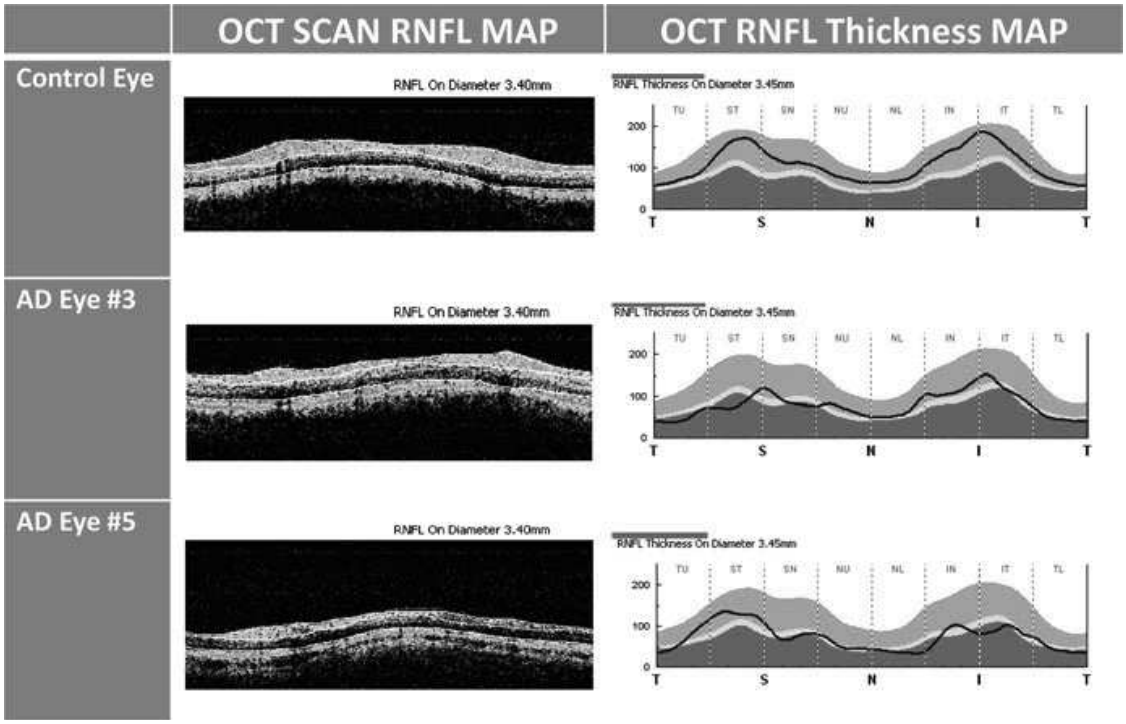

Fig. 7.1 Optical Coherence Tomography (*OCT*) imaging taken in cylindrical section of tissue surrounding the optic disc of a control eye and of 2 AD patients eyes. The images in the *left panel* are raw OCT data, while the maps in the *right panel* are quantitative data curve. In AD patients eyes OCT shows a decrease of RNFL reflection (reduced RNFL thickness) in each examined quadrant, with particular prevalence of the temporal ones

et al. [82] found no differences in the regional distribution of RNFL thickness between patients with mild to moderate AD and healthy controls evaluated with scanning laser polarimetry. The same researchers did not observed optic nerve head structural abnormalities in AD by using real-time topographical images obtained with a Heidelberg retina tomograph (HRT) from individuals in the early stages of AD compared with age-matched controls [83].

Berisha et al. [71] tried to determine whether regional thinning of the RNFL occurred in the nine patients with mild to moderate AD and to determine whether the retinal circulation was abnormal in these patients. AD patients showed a marked narrowing of the retinal venous blood column diameter and a reduction in retinal blood flow rate compared with eight age-matched control subjects. OCT data confirmed a significant thinning of the peripapillary RNFL that was most pronounced in the superior quadrant, which did not correlate with the retinal blood flow [71]. They argued that the mechanisms producing reduced blood flow in the retina are related to those that produce cerebral blood flow abnormalities, which are known to occur in AD, such as increased venous wall thickness due to collagen and β-amyloid deposition [84].

In a cross-sectional study on 150 patients with low-to-moderate dementia and 61 controls, researchers compared the parameters provided by two commercially available spectral domain OCT devices, the Cirrus and the Spectralis OCT instruments

Table 7.1 Demographic data and RNFL thickness measurements in patients and controls as determined by OCT

Reference	No. of subjects and diagnosis	Mean MMSE/ AD stage	Mean age ± SD	OCT machine	Mean RNFL (μm)	Superior quadrant (μm)	Inferior quadrant (μm)	Nasal quadrant (μm)	Temporal quadrant (μm)	Note
Parisi et al. [68, 69]	17 AD 14 controls	/mild	70.37 ± 6.1	Humphrey	59.5 ± 16.70[a] 99.9 ± 8.95	72.1 ± 21.4[a] 104.6 ± 12.1	77.9 ± 26.4[a] 116.2 ± 9.87	50.4 ± 23.2[a] 93.4 ± 13.7	37.9 ± 17.60[a] 85.6 ± 8.21	RNFL overall values correlated with PERG
Iseri et al. [70]	14 AD 15 controls	18.5/mild to moderate 29.4	70.1 ± 9.7 65.1 ± 9.8	Carl Zeiss Meditec, Model 3000	87.4 ± 23.7[a] 113.1 ± 6.7	112.6 ± 35.3[a] 137.1 ± 16.4	103.1 ± 33.6[a] 141.5 ± 19.1	63.5 ± 19.1[a] 96.0 ± 34.4	64.9 ± 17.7 72.3 ± 16.4	Decline in both peripapillary and macular thickness and volume in AD eyes
Berisha et al. [71]	9 AD 8 HV	23.8/mild to moderate 29.5	74.3 ± 3.3 74.3 ± 5.8	Carl Zeiss Meditec, Model 3000		92.2 ± 21.6[a] 113.6 ± 10.8	117.0 ± 15.3 128.1 ± 11.4	67.0 ± 15.0 69.5 ± 11.1	65.7 ± 15.1 64.1 ± 7.3	Narrowing of the retinal microvasculature
Paquet et al. [72]	23 MCI 14 AD 12 AD 15 controls	28.8 22.6/mild 16.6/ severe 28.9	78.7 ± 6.2 78.3 ± 5.1 78.8 ± 4.9 75.5 ± 5.1	Carl Zeiss Stratus OCT 3	89.3 ± 2.7[a] 89.2 ± 2.9[a] 76.6 ± 3.8[a] 102.2 ± 1.8					The involvement of retina is an early event in the course of this disorder
Lu et al. [59]	22 AD 22 controls		73 ± 8 68 ± 9	Carl Zeiss Meditec, Model 3000	90 ± 18[a,b] 98 ± 12	107 ± 30[a,b] 124 ± 16	116 ± 35[a,b] 128 ± 18	66 ± 26 70 ± 17	70 ± 20 71 ± 13	Enlarged optic cup to disc ratio in AD
Kesler et al. [73]	24 MCI 30 AD 24 controls	28.1 23.6	71.0 ± 10.0 73.7 ± 9.9 70.9 ± 9.2	Carl Zeiss Stratus OCT 3	85.8 ± 10.0[a] 84.7 ± 10.6[a] 94.3 ± 11.3	101.3 ± 15.2 99.0 ± 18.0[a] 110.0 ± 16.7	111.9 ± 16.1[a] 110.1 ± 19.1[a] 127.0 ± 15.5	65.9 ± 15.1 66.8 ± 14.5 76.4 ± 21.8	64.2 ± 13.9 61.7 ± 10.9 67.8 ± 15.1	RNFL thickness not correlated with MMSE

Kromer et al. [74, 75]	22 AD 22 controls	22.6/mild to moderate	75.9 ± 6.1 64.0 ± 8.2	Spectralis Heidelberg Engineering	80[b,c]	46[b,c]		47[b,c]		The RNFL of the AD patients did not correlate with pattern VEP latencies.
Moreno-Ramos et al. [76]	10 AD 10 LB 10 PD 10 controls	16.4 14.9 16.4 29.2	73.0 ± 6.5 74.2 ± 5.1 74.3 ± 5.0 70.2 ± 5.5	TOPCON 3D OCT-1000	94.5 ± 2.2[a] 93.3 ± 1.5[a] 94.8 ± 2.0[a] 108.0 ± 2.2					Retinal involvement measured by OCT may also be present in non-AD dementias
Marziani et al. [77]	21 AD 21 controls	19.9/mild to moderate 27.9	79.3 ± 5.7 77.0 ± 4.2	(1) Optovue RTVue-100 & (2) Spectralis Heidelberg Engineering	244.1 ± 17.9[1] 277.5 ± 21.7[2] 252.3 ± 19.2[1] 283.8 ± 27.3[2] Central sector	274.8[1a,d] 304.3[2a,d] 288.9[1d] 319.3[2d]	273.25[1a,d] 301.7[2a,d] 286.25[1d] 314.75[2d]	278.4[1a,d] 309.35[2a,d] 290.85[1d] 323.55[2d]	271.8[1a,d] 291.95[2a,d] 286.25[1d] 304.45[2d]	Reduced RNFL in AD patients using 2 different OCT instruments
Kirbas et al. [78]	40 AD 40 controls	21.5	69.3 ± 4.9 68.9 ± 5.1	Spectral domain OCT	65 ± 6.2[a] 75 ± 3.8	76 ± 6.7[a] 105 ± 4.8	106 ± 11.5 108 ± 8.7	75 ± 2.8 76 ± 2.7	74 ± 6.7 77 ± 7.3	No correlation between MMSE and OCT results
Larrosa et al. [79]	151 AD 61 controls	18.31	75.29 74.87	(1) Carl Zeiss Meditec Cirrus & (2) Spectralis Heidelberg Engineering	97.5 ± 14.1[1] 98.2 ± 17.1[2a] 100.5 ± 13.0[1] 102.7 ± 6.7[2]	113.2 ± 18.7[1a] 117.8 ± 19.0[1a]	120.4 ± 20.1[1a] 127.4 ± 21.0[1]	72.7 ± 17.3[1] 74.5 ± 17.2[1]	64.5 ± 21.7[1a] 67.8 ± 20.0[1]	RNFL measurements were a very useful and precise tool for AD diagnosis.

(continued)

Table 7.1 (continued)

Reference	No. of subjects and diagnosis	Mean MMSE/ AD stage	Mean age ± SD	OCT machine	Mean RNFL (μm)	Superior quadrant (μm)	Inferior quadrant (μm)	Nasal quadrant (μm)	Temporal quadrant (μm)	Note
Ascaso et al. [80]	21 aMCI 18 AD 41 controls	19.3 28.8	72.1 (AD + aMCI) 72.9	Stratus OCT 3	86.0 ± 7.2[a] 64.7 ± 15.2[a,e] 103.6 ± 8.9 (data showed from the right eye only)	96.7 ± 14.6[a] 73.2 ± 22.0[a,e] 126.6 ± 13.8	110.1 ± 17.7[a] 86.2 ± 25.7[a,e] 135.6 ± 17.6	71.0 ± 16.7[a] 43.3 ± 20.4[a,e] 77.8 ± 16.7	66.3 ± 12.1[a] 56.7 ± 14.9[a,e] 75.8 ± 16.6	A significant association between RNFL thickness in superior and nasal quadrants, and MMSE score

AD Alzheimer's disease, *aMCI* amnestic mild cognitive impairment, *LB* dementia with Lewy bodies, *MCI* mild cognitive impairment, *MMSE* mini mental state examination, *RNFL* retinal nerve fiber layer, *PD* dementia associated with Parkinson's disease

[a]Significantly different from controls

[b]Data extrapolated from the bar chart

[c]Statistics do not clearly show

[d]Mean of internal plus external sectors

[e]Significantly different from MCI

[1,2]OCT machine

[79]. With both devices, they confirmed the retinal thinning in AD patients, and they found that the best parameter for distinguishing AD patients from healthy controls using OCT measurements was the Spectralis looking at RNFL [79]. Along these lines, Marziani et al. [77] used both Optovue RTVue-100 and Spectralis instruments to evaluate retinal thickness in 21 patients affected by AD in comparison with 21 healthy controls. Both instruments showed a significant difference in full retinal thickness between patients and controls in all the macular sectors except in the central sector and for the superior external sector [77].

In order to verify whether involvement of the retina is an early event in the course of AD, few studies compared MCI versus AD patients and healthy aged people. Paquet and coworkers [72] enrolled 23 MCI patients, 14 mild AD, 12 moderate to severe AD patients, and 15 healthy subjects. Overall, mean RNFL thickness was reduced in all patient groups in respect to controls. The subgroup analyses revealed no difference between the results observed in MCI and in mild AD patients, whereas RNFL thickness assessed in moderate to severe AD patients was significantly reduced in respect with that assessed in MCI patients [72]. Kesler et al. [73] obtained similar results finding that the mean RNFL was significantly thinner in both AD and MCI patients groups compared to controls, and that the MCI group fell in between the other two groups. This difference was particularly prominent in the inferior quadrant, whereas the AD patients had significantly thinner retinal NFL values also in the superior quadrant [73].

Recently, investigators attempted to identify individuals who might be at a high risk of developing AD, and observed that, despite the reduction in peripapillary RNFL thickness, central 1-mm foveal thickness and macular volume were significantly increased in aMCI patients, but not in AD patients, when compared with age-matched controls. The authors argued that retinal swelling might be the first sign of macular retinal ganglion cell degeneration probably due to inflammation and/or gliosis in the early stages of AD [80].

Finally, it is worth noting that thinning of RNFL is also present in other types of dementia, such as dementia with Lewy bodies, dementia associated with Parkinson's disease [76] and with cerebral autosomal dominant arteriopathy with subcortical infarcts and leuco-encephalopathy (CADASIL) [85] challenging the specificity of OCT findings in AD patients.

7.4 Structural-Functional Correlations

The functional activity of the visual system can be dissected by the use of electrophysiological techniques such as pattern electroretinogram (PERG) and visual evoked potentials (VEPs) that have the capability of assessing, respectively, the bioelectrical activity of retinal ganglion cells and their fibers, and the functional integrity of the entire visual pathways from retina to the visual cortex.

The implicit times were delayed and/or the amplitudes reduced [68, 69, 86–89] in most of the PERG studies performed in AD patients at various stages, reflecting

retinal ganglion cell dysfunction. However, in some studies PERG parameters were within the range of normality [90, 91]. In one study luminance pattern ERGs were delayed and amplitudes reduced, whereas isoluminant chromatic ERGs were always within the normal ranges [89].

The implicit time of patterned VEP was normal in some studies [86, 89, 92, 93] and in others delayed [88, 91, 94, 95], with the amplitudes within the range of normality. A delayed P2 component of the flash VEP is a common finding across studies in AD patients [86, 92, 96, 97], with one exception [94].

Taken as a whole, these electrophysiological results are consistent with the early histological studies showing retinal ganglion cell dysfunction in AD [12, 22] and supports the notion that this damage in AD preferentially affects the larger, faster-conducting retinal ganglion cells and their retinocortical projections.

Parisi and coworkers [68, 69] used OCT and PERG in a group of 17 mild severity AD patients compared with a group of 14 healthy controls. They observed that the general reduction of peripapillary RNFL thickness was accompanied with delayed N35, P50 and N95 implicit times and reduced N35-P50 and P50-N95 amplitudes in their AD patients. More interestingly, in AD eyes, the RNFL overall values were positively correlated to the PERG P50 and N95 implicit times and PERG P50-N95 amplitude. This was not so in controls [68, 69]. However, Iseri et al. [70] did not find significant differences in VEP P100 implicit times and N75-P100 amplitudes recorded at high spatial frequency in a group of 14 mild to moderate AD patients when compared with a group of 15 controls. Moreover, they saw no correlation between any of the abnormally in RNFL and macular OCT thickness and VEP in AD [70]. This negative correlation, between VEPs parameters recorded at both high and low spatial frequency and OCT peripapillary scans, was later corroborated [75].

7.5 Correlations with Psychometric Measures

Along with personal history, physical examination and laboratory tests, questionnaires are often used to help test a range of everyday mental skills of persons with symptoms of dementias. Widely used tests include the mini mental state examination (MMSE), the Alzheimer's disease assessment scale- (ADAS-Cog), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

The previously mentioned parameters of increased cup-to-disc ratio, cup volume, and decreased optic disc rim area, all found in AD patients by optic nerve analyser, positively correlated with ADAS-Cog scores and disease's duration [57]. Moreover, the reduced total macular volume in patients with AD was positively correlated with the severity of the disease as assessed by the MMSE [70, 76]. However, other studies failed to find the same associations [72–75, 78]. RNFL thickness of AD or MCI patients was non associated with other patient demographic features, such as age [72, 79], gender, and AD stage [74].

In AD patients, but not in aMCI, multiple linear regression models showed a strong association between overall RNFL thickness and MMSE score. The same

association was found between MMSE and RNFL thickness in superior and nasal quadrants. Macular thickness and volume were not associated with MMSE score either in aMCI or in AD patients [80].

A prospective study attempted to determine whether deterioration of patients' cognitive functions, as verified with the RBANS test, correlated to specific OCT findings [98–100]. These investigators followed, for a period of 25 months, two groups of subjects: 82 participants with a normal cognitive status and 22 MCI patients. The participants who completed the observational period were further categorized as 60 participants experiencing a stable cognitive status and 18 participants who experienced a worsening of their cognitive status. The investigators found that in those participants who remained stable, greater attenuation of RNFL in the superior quadrant could predict specific cognitive deteriorations. In contradistinction, in participants who worsened, less attenuation of RNFL in the inferior quadrant could predict greater cognitive deterioration [98–100]. These findings suggest that patients who have less reduction in the thickness of the inferior quadrant of RNFL over time may have a higher risk of developing MCI and dementia, leading the authors to put forward RNFL thickness as a potential biomarker of dementia.

7.6 Conclusions

The diagnosis of AD is often based on psychometric assessments by a multidisciplinary team (neurologists, psychiatrists, and psychologist) and an objective neurological examination. Because of inter- and intra-individual variability, neurophysiological and neuroimaging tests have not yet been considered as criteria on which to base a diagnosis. In fact, neurophysiological as well as other paraclinical tests are recommended only on suspicion of secondary causes of dementia as part of the differential diagnosis of AD. The AD diagnosis is confirmed only with *post mortem* histopathology. Nonetheless, the last few decades have seen the use of structural and functional techniques as potential biomarkers that might also identify factors that may predispose individuals to AD. The optical coherence tomography (OCT) technique for the measurement of the peripapillary RNFL, the macular thickness and volume, has been demonstrated as useful for the demonstration of significant retinal changes in patients that roughly correlate with the severity of the disease (Fig. 7.2).

Particularly intriguing results of recent experiments include:

- In both animal models, expressing mutant forms of amyloid precursors, and histological studies on *post mortem* AD eyes, researchers have observed various retinal pathological changes, such as accumulation of Aβ aggregates within the retina and its microvasculature, retina ganglion cell death and signs of neuroinflammation.
- In evaluations with the optic nerve analyser, a higher proportion of AD patients show signs of optic neuropathy manifesting as optic disc atrophy, pathologic optic disc cupping, and thinning of the neuroretinal rim and of the RNFL.

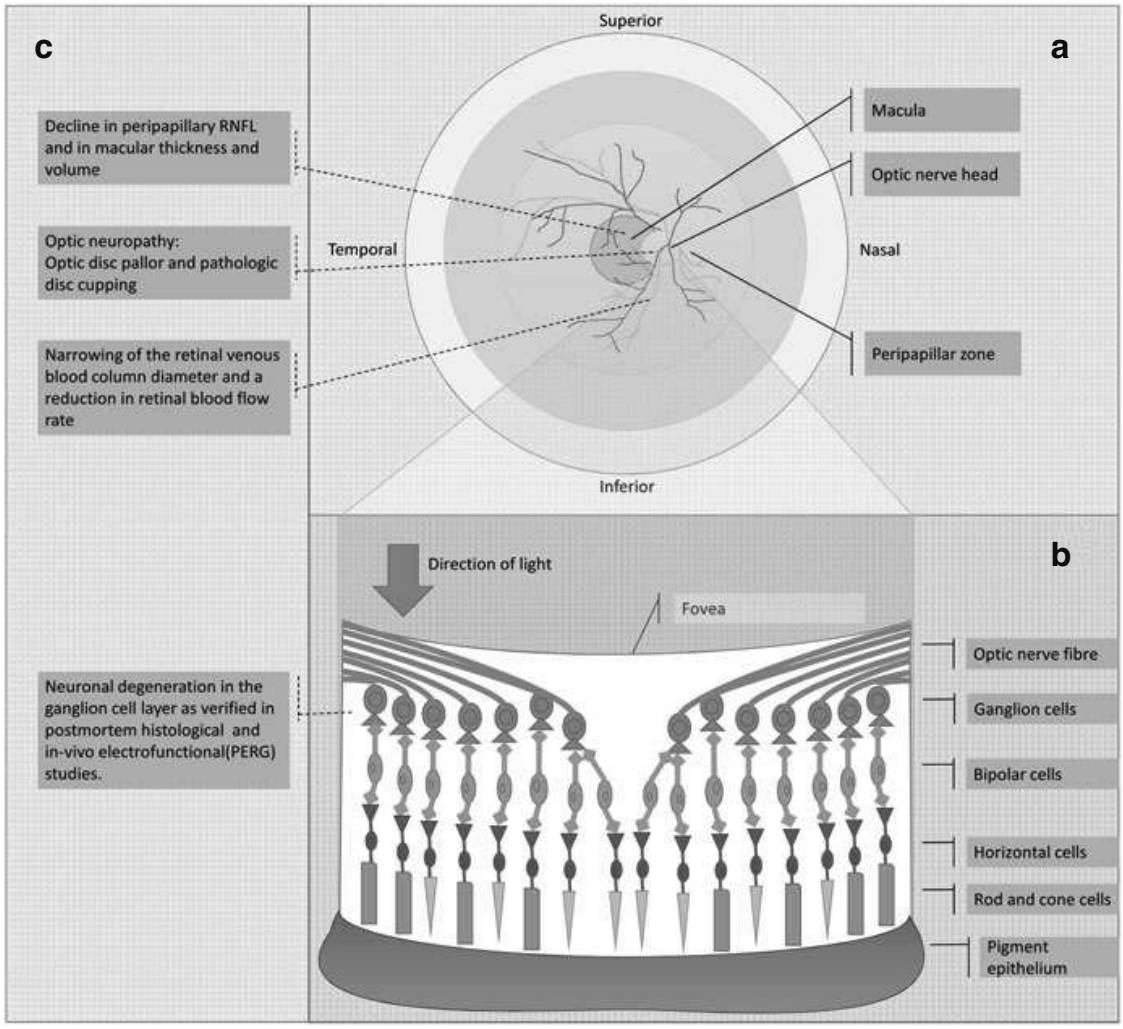

Fig. 7.2 Schematic representation of an entire retina with superimposed anatomic zones (*upper panel* **a**) and a schematic enlargement of a portion of the retina with the main cell classes (*lower panel* **b**). On the *left panel* (**c**) are summarized the findings from the OCT and electrophysiological studies in AD

- In agreement with *post mortem* studies, OCT data studies indicate a significant decline in peripapillary RNFL and also changes in macular thickness and volume that is progressive from MCI to AD eyes.
- Electrophysiological and OCT studies in AD patients show RNFL thickness reduction that is related to neuronal degeneration in the retinal ganglion cell layer that is not a consequence of retrograde degeneration from the post-chiasmatic visual pathway.
- The correlations between morphological and clinical features tend to suggest a potential role for optic nerve head analysis in monitoring the progression of AD and as outcome measures in the assessment of any purported AD treatments.

Overall, these results suggest that degeneration of the retinal ganglion cells should be added to the constellation of neuropathologic changes found in patients with Alzheimer's disease.

Other neurodegenerative disorders, like Parkinson's disease and glaucoma, may enter in the differential diagnosis of RNFL thinning [101]. A particular mention merits the controversial association between primary open angle glaucoma (POAG) and AD. This is based on various indirect evidence of some shared genetic, histopathological and functional features [102, 103]. However, even not considering the prevalent involvement of cognitive areas, especially of the hippocampus, that accompanies AD respect neurodegenerative processes confined to the visual pathway of POAG, the mutual association of the two clinical entities is poorly supported by conflicting epidemiological studies [104, 105].

Future research in this subject area will include a better assessment of the specificity of these OCT findings in AD. We will see RNFL thickness measurements in patients with vascular dementia as an aide to diagnosis and we will see whether the RNFL can be used as a surrogate for magnetic resonance imaging measurements of the brain. These and similar studies will use OCT parameters of retinal changes as criteria against which to measure new molecules purported to help in the treatment of AD.

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Chapter 8
Friedreich's Ataxia and More: Optical Coherence Tomography Findings in Rare Neurological Syndromes

Chiara La Morgia and Michele Carbonelli

Abstract Optic nerve and retinal involvement are a frequent finding in many neurodegenerative disorders. Optic atrophy can be severe and diffuse or sectorial and can be associated with visual complaints and reduction of visual acuity.

We here report the main optical coherence tomography (OCT) findings in rare neurological syndromes for which OCT data are available.

In Friedreich's ataxia, which is an autosomal recessive disease, there is evidence of subclinical optic neuropathy. OCT studies describe a diffuse reduction of the retinal nerve fiber layer (RNFL) thickness without a specific and preferential involvement of the papillo-macular bundle.

Jansky-Bielschowsky disease is a late infantile neuronal ceroid lipofuscinosis characterized by both retinal and optic nerve atrophy. Only one OCT study is available describing retinal abnormalities of various degrees.

DNA (cytosine-5)-methyltransferase 1 (DNMT1) disease is an autosomal dominant multisystem disorder characterized by the association of narcolepsy, deafness, sensory neuropathy and optic atrophy. The only OCT study available from our group describes the presence of subclinical optic atrophy more evident in the temporal quadrant.

Hereditary spastic paraplegia due to *SPG7* mutation is an autosomal recessive neurodegenerative disorder characterized by spastic paraparesis. RNFL thinning is a frequent and consistent finding in this disease.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant disorder in which retinal vascular changes and neurodegeneration of the neuroretina are frequent findings.

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Wolfram's disease is a disorder characterized by the occurrence of diabetes mellitus and optic atrophy. The only two OCT studies available report a diffuse optic atrophy which leads to a severe reduction of visual acuity.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a hereditary spastic ataxia due to progressive degeneration of the cerebellum and spinal cord, characterized by retinal nerve fiber hypertrophy detected by OCT.

Spinocerebellar ataxias (SCAs) are heterogeneous genetically determined disorders for which OCT studies available show variable findings ranging from isolated thinning of the temporal RNFL to retinal photoreceptor abnormalities.

Keywords Optical coherence tomography • Optic nerve • Retina • Macula • Fundus • Friedreich's ataxia • Jansky-Bielschowsky • Neuronal ceroid lipofuscinosis • DNMT1 • SPG7 • Cadasil • Wolfram syndrome • Autosomal recessive spastic ataxia of Charlevoix-Saguenay • Spinocerebellar ataxias

8.1 Friedreich's Ataxia

Friedreich's ataxia (FA) is an autosomal recessive slowly progressive neurodegenerative disorder starting usually in young adulthood or childhood [1]. FA is characterized by spinocerebellar and sensory ataxia with absence of deep tendon reflexes, dysarthria, hypertrophic cardiomyopathy and scoliosis [2]. FA is due to a GAA triplet expansion in the first intron of the frataxin gene (FXN) on chromosome 9q13-q21.1. A minority of FA patients are compound heterozygotes for the GAA triplet expansion and a point mutation [3].

Frataxin is a mitochondrial protein with a crucial role in the insertion of Fe-S cluster in different enzymes of the mitochondrial respiratory chain and in particular complex I, II and III and aconitase [4, 5]. The abnormal function of FXN leads to dysregulation of cellular iron metabolism with mitochondrial accumulation [6]. Evidence of mitochondrial defective respiration has been demonstrated in the heart and muscle of FA patients [7, 8]. Recent studies demonstrated that mitochondrial dysfunction induced by frataxin is also related to abnormal calcium handling in the mitochondria leading to increased autophagy [9]. Overall, frataxin deficiency leads to abnormal iron homeostasis [10] and increased oxidative stress [11, 12].

Visual system involvement is well characterized in FA [13]. In particular, abnormalities of the visual efferent system such as fixation instability (square wave jerks), saccadic dysmetria, disrupted pursuit, and vestibular abnormalities have been reported [13]. Moreover, optic neuropathy, optic radiation abnormalities and retinitis pigmentosa have been described in FA patients [14–19].

The optic neuropathy described in FA is usually asymptomatic and does not affect central vision [16]. The most severe visual phenotype has been associated with large GAA expansion of the FTX gene and with compound heterozygous mutations [16]. Visual evoked potentials demonstrated delayed latency and reduced