Differential Diagnosis of Age-Related Macular Degeneration

Differenzialdiagnose der altersabhängigen Makuladegeneration

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ABSTRACT

A diagnosis of age-related macular degeneration (AMD) may have a significant impact on a patient's life. Therefore, it is important to consider differential diagnoses, as these can differ considerably from AMD regarding prognosis, inheritance, monitoring and therapy. Differential diagnoses of AMD include other macular diseases with drusen, drusen-like changes, monogenic retinal dystrophies, as well as a range of other, often rare macular diseases. In this review, clinical examples are presented that illustrate alternative diagnoses to AMD and when these should be considered. These include, amongst others, patients with autosomal dominant drusen, Sorsby fundus dystrophy, pachydrusen, late-onset Stargardt disease, extensive macular atrophy with pseudodrusen (EMAP), pseudoxanthoma elasticum (PXE), North Carolina macular dystrophy, mitochondrial retinopathy, benign yellow dot maculopathy, dome- or ridge-shaped maculopathy, or macular telangiectasia type 2.

ZUSAMMENFASSUNG

Die Diagnose der altersabhängigen Makuladegeneration (AMD) kann einen Einschnitt im Leben von Patienten bedeuten. Vor diesem Hintergrund ist es wichtig, Differenzialdiagnosen in Erwägung zu ziehen, da diese sich hinsichtlich Prognose, Vererblichkeit, Kontroll- und Therapiebedarf beträchtlich von der AMD unterscheiden können. Differenzialdiagnosen sind vor allem andere Makulaerkrankungen mit Drusen, drusenähnlichen Veränderungen, weitere monogene Netzhautdystrophien sowie ein breites Spektrum weiterer, oftmals seltener Makulaerkrankungen. In dieser Übersicht werden anhand klinischer Beispiele Befundkonstellationen gezeigt, bei denen eine Differenzialdiagnose der AMD in Erwägung gezogen werden sollte. Unter anderem beinhaltet dies Patienten mit autosomal-dominanten Drusen, Sorsby-Fundusdystrophie, Pachydrusen, spät beginnendem Morbus Stargardt, extensive makuläre Atrophie mit Pseudodrusen (EMAP), Pseudoxanthoma elasticum (PXE), North-Carolina-Makuladystrophie, mitochondriale Retinopathie, Benign Yellow Dot Maculopathy, kuppel- oder leistenförmige Makulopathie und makuläre Teleangiektasien Typ 2.

Introduction

Age-related macular degeneration (AMD) is one of the most common retinal diseases and a major cause of mild to severe visual impairment in old age [1, 2]. A diagnosis of AMD often leads to uncertainty with regards to future planning, as associated problems with vision can have a substantial impact on everyday life as well as quality of life [3, 4]. As other retinal diseases may have similar symptoms and morphological alterations it is important to consider differential diagnoses for the following reasons:

1. Prognosis and progression to advanced disease – atrophy and/or exudative neovascularisation – may vary considerably, which could play a major role in patient counselling, follow-up examination frequency, emotional burden, and treatment regime.
2. Treatment specifically targeting AMD pathophysiology would expose patients to the risk of side effects and complications of therapy, without the expected benefit, if the underlying diagnosis is not AMD.
3. AMD misdiagnosis may lead to patients being denied treatment specific for their condition, if such a treatment is available.
4. Early detection of other systemic clinical symptoms might be missed.
5. Assessment of heritability may vary greatly depending on diagnosis.

General Differential Diagnostic Considerations

Functional changes and reported symptoms often have limited importance in formulating a differential diagnosis in routine clinical practice: reduced visual acuity, blurred vision, reading difficulties, central and paracentral scotomas, and dark adaption problems can occur in patients with AMD and in other macular diseases, although patients can be completely asymptomatic in the early stages. However, some symptoms occur especially frequently in certain diseases. These include reading difficulties without other symptoms as observed in patients with macular telangiectasia type 2 (MacTel), and initial dark adaptation problems in patients with Sorsby fundus dystrophy (SFD), late-onset retinal degeneration (LORD), and pseudoxanthoma elasticum (PXE).

Of particular importance is the general medical history. Systemic diseases or manifestations are often not recognised by patients to be associated with their ocular changes; the use of certain medications and the medical histories of other family members may also point to other differential diagnoses, although AMD also often occurs at higher frequency in families. Clinical examination and multimodal retinal imaging are especially important to detect alternative diagnoses for AMD in the following diagnostic situations:

1. Atypical findings
2. Absence of drusen, normally a characteristic feature of AMD
3. Young age relative to phenotypic severity

The following overview presents differential diagnoses for AMD, although this article is not intended to be exhaustive owing to the wide range of (rare) macular diseases. The examples should rather serve to raise awareness of certain phenotypic patterns indicating a diagnosis other than AMD.

▶ **Table 1** Selected differential diagnoses for AMD grouped according to key findings. The right column shows the estimated risk of developing macular neovascularisation (MNV). Diseases cannot be unequivocally assigned to a particular key finding in many cases, so these categories are intended as a guide.

Key findings	Disease	MNV risk
Drusen – different subtypes	Basal laminar drusen (BLD)	+
	Drusen in systemic complement activation	+
	Autosomal dominant drusen	+
	Sorsby fundus dystrophy (SFD)	++
	Late-onset retinal degeneration (LORD)	+
	Extensive macular atrophy with pseudodrusen (EMAP)	+
	Pseudoxanthoma elasticum (PXE)	+++
	Pachydrusen	+
Drusen-like changes and vitelliform lesions	Macular dystrophy with spots and/or dots	–
	Macular dystrophy with vitelliform lesion	+
	Non-monogenic vitelliform lesions	+
	North Carolina Macular Dystrophy (NCMD)	+
	Benign yellow dot maculopathy (BYDM)	–
	Primary hyperoxaluria	–
Other monogenic diseases	Macular dystrophies and cone dystrophies	–
	Mitochondrial retinopathy	–
	Choroideraemia carrier	–
Other macular diseases	Macular telangiectasia type 2 (MacTel)	+
	Central serous chorioretinopathy (CSC)	+
	Myopic maculopathy	+
	Pseudoxanthoma elasticum (PXE)	+++
	Dome-shaped maculopathy	–
	HCQ retinopathy	–
	Congenital rubella retinopathy	–
	Deferoxamine-associated retinopathy	–
	Juxtapapillary choroidal neovascularisation (CNV)	+
	Post-inflammatory changes	++

To facilitate a differential diagnosis based on the clinical presentation, certain key findings may be used as guidance (▶ **Table 1**). Even if certain characteristics can be typical for a particular disease, there are often phenotypic overlaps: for example, patients with PXE may initially present with reticular pseudodrusen or mainly pigmentary abnormalities; patients with SFD may present with drusen or macular neovascularisation. There is also room for interpretation in evaluating clinical findings, so these categories are only intended as a guide.

Chorioretinal atrophy is a characteristic finding in late stages of some (but not all) macular diseases, so determining a differential

diagnosis may be difficult at this stage. However, alterations outside the atrophy may provide clues to the particular diagnosis. Neovascularisation may occur in most AMD differential diagnoses, albeit with varying likelihoods (▶ **Table 1**).

Age-related macular degeneration (AMD)

AMD covers a spectrum of retinal changes; awareness of these alterations plays a major role in whether to consider a further differential diagnosis (▶ **Fig. 1**). Early AMD can exhibit several signs including macular drusen, hypopigmentation, and hyperpigmentation. Drusen subtypes include soft drusen, basal laminar drusen, and reticular pseudodrusen. Late AMD can manifest in two distinct forms – atrophic or "dry" AMD characterised by geographic atrophy, and neovascular or "wet" AMD. Atrophic AMD (dry AMD) exhibits atrophy of the photoreceptor-RPE-choriocapillaris complex, with initial involvement occurring around or radiating from the fovea. Neovascular AMD has several sub-forms: Neovascularisation below the RPE – "occult" choroidal neovascularisation (CNV) – which is typical of type 1 macular neovascularisation (MNV); type 2 or classic CNV with neovascularisation between the RPE and photoreceptors; and type 3 with initial neovascularisation assumed to originate from the retinal vascular network – retinal angiomatous proliferation, or RAP. Another distinctive phenotype is polypoidal choroidal neovascularisation (PCV), a variant of type 1 MNV; however, its relationship with typical AMD remains a matter of controversy. There are also mixed forms of neovascular AMD. Overall, clinical AMD features are heterogeneous, which is not surprising in a genetically complex disease influenced by environmental parameters. However, the complex genetics of AMD will not be discussed further here.

Diseases with Drusen

Basal laminar drusen (BLD)

The main clinical difference between this manifestation and AMD is the – at least initial – presentation with pure BLD. The literature sometimes uses alternative terms for BLD such as *cuticular drusen, diffuse drusen* and *early adult onset, grouped drusen*. BLD do not differ significantly in location, molecular composition, or structure from typical soft drusen in AMD [5], but are smaller and usually present in larger numbers (▶ **Fig. 2a**). Soft drusen and/or RPD also develop more frequently over time. There is evidence that BLD pathophysiology is very similar to AMD but exhibits a more pronounced genetic aspect with variants in genes encoding components in the complement system; this may explain the disease's earlier onset [6].

OCT examination usually shows a sawtooth-like pattern, and fluorescein angiography shows a window defect associated with each druse ("stars in the sky") due to focal thinning in the retinal pigment epithelium [6]. Even so, diagnosis does not require angiographic examination. Vitelliform lesions may also develop as a typical manifestation in BLD; these usually progress to atrophy [7].

Drusen in systemic complement activation

The cross-over between typical AMD, BLD and drusen associated with primary systemic complement activation appears to be gradual, as a genetically determined dysregulation of complement activation also occurs in AMD and BLD. Systemic complement hyperactivation may also occur in patients with type 2 membranoproliferative glomerulonephritis (MPGN2), which indicates that renal function testing should be considered in patients with early-onset drusen (usually BLD). HIV infection may also lead to increased complement pathway activation; however, there has so far been limited evidence of any association with drusen (▶ **Fig. 2b**).

Pachydrusen

Pachydrusen may be observed in diseases of the pachychoroid spectrum, which share specific choroidal changes. A thickened choroid and dilated choroidal vessels may be detected on OCT imaging. OCT angiography also often reveals reduced choriocapillaris structure [8]. Pachydrusen may occur solitary or in groups and may differ from the often smooth-convex drusen shape with a rather 'angular' appearance (▶ **Fig. 2c**). Pachydrusen may be observed together with other findings seen in pachychoroid disease, such as subretinal fluid, occult neovascularisation, and peripapillary intraretinal fluid.

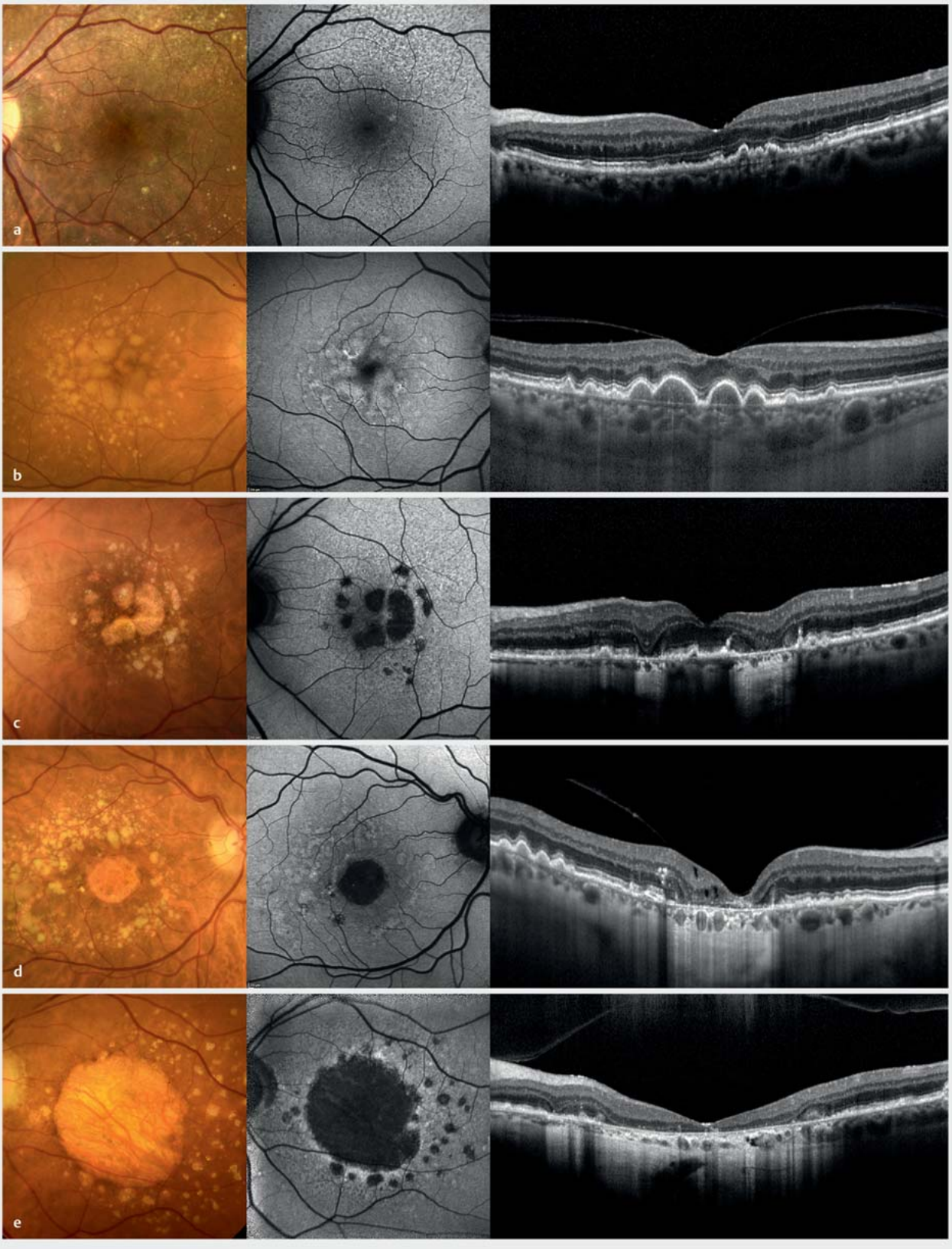
Autosomal dominant drusen

Autosomal dominant drusen are also referred to as *Doyne honeycomb dystrophy* or *Malattia Leventinese*. These historical names refer to the same disease caused by a specific point mutation in the *EFEMP1* gene [9]. Due to variable expressivity, retinal changes may vary considerably even within families and at similar ages [10].

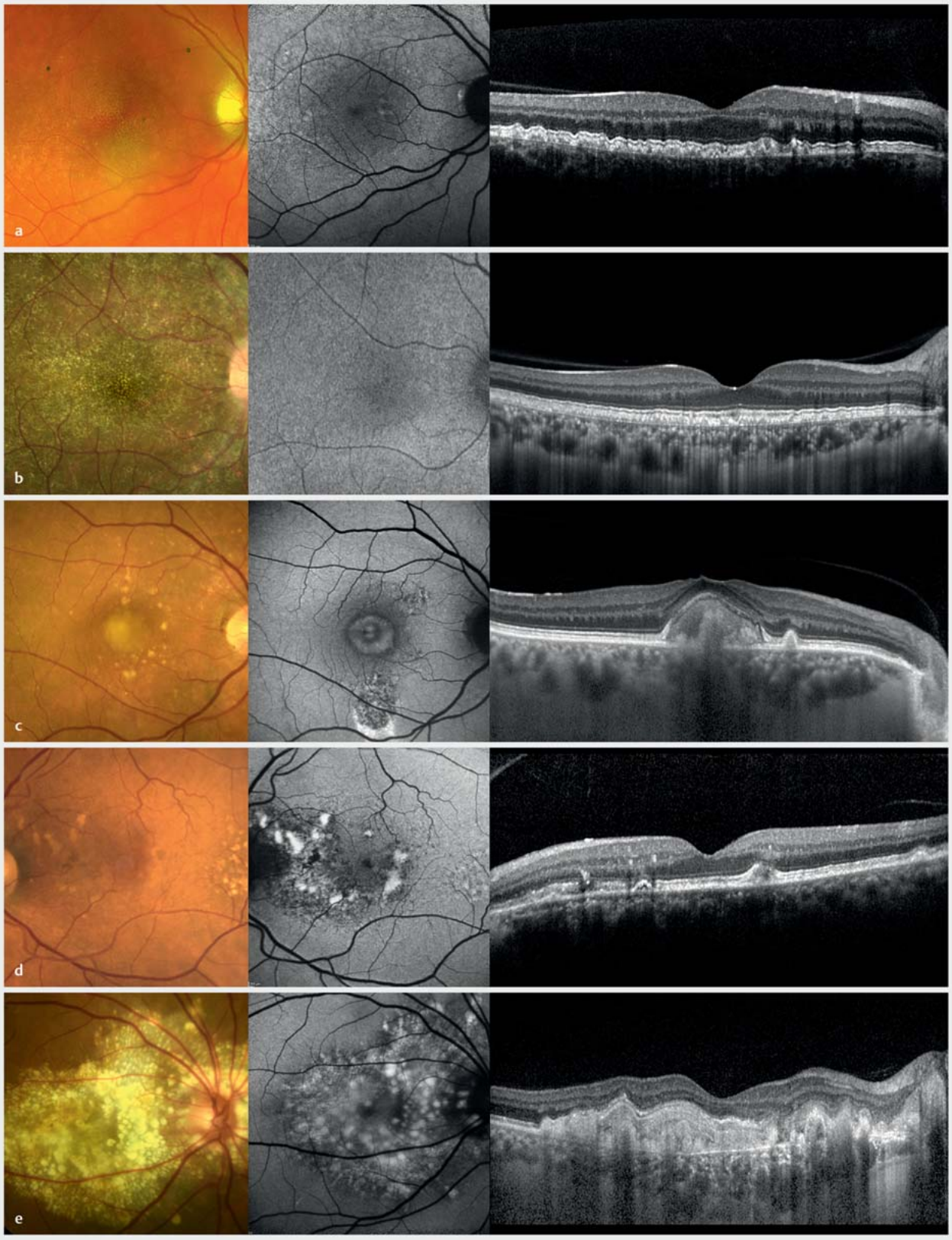
Two findings have often been reported to be characteristic for autosomal dominant drusen – nasal, peripapillary drusen, and a radial-centrifugal drusen arrangement at the posterior pole. The drusen typically show increased autofluorescence (▶ **Fig. 2d**, **e**).

Sorsby fundus dystrophy (SFD)

SFD is caused by mutations in the tissue Inhibitor of metalloproteinase 3 (*TIMP3*) gene and follows an autosomal dominant inheritance pattern. First symptoms often include rapid visual acuity changes when MNVs develop or vision problems in dimmed light conditions. Many patients experience initial vision problems in the 4th or 5th decade of life, but first symptoms may also be experienced in the age range of AMD patients. In early disease stages, drusen of various subtypes may occur, especially reticular pseudodrusen. As the disease progresses, chorioretinal atrophy and MNVs or subretinal fibrosis typically occur (▶ **Fig. 3a**) [11, 12]; the latter may also appear in eyes without drusen. Family history with an autosomal dominant inheritance pattern plays an important role in the differential diagnosis. TIMP3 is expressed systemically, especially in the lungs, so an association with changes in the lung (bronchiectasis) observed more frequently in SFD patients seems logical [13].



▶ **Fig. 1** Representative images from patients with age-related macular degeneration using fundus photography, fundus autofluorescence, and optical coherence tomography (OCT), from left to right. **a**, **b** patients with early or intermediate AMD. **c**–**e** patients with geographic atrophy. Age of patients (in years): **a:** 78; **b:** 77; **c:** 86; **d:** 77; **e:** 81.



▶ **Fig. 2** Differential diagnoses of age-related macular degeneration – diseases characterised by drusen. Left to right: Fundus photography, fundus autofluorescence, optical coherence tomography (OCT). **a** Basal laminar drusen. **b** Drusen in HIV. **c** Pachydrusen. **d–e** Autosomal dominant drusen. Age of patients (in years): **a:** 57; **b:** 35; **c:** 71; **d:** 82; **e:** 64.

Late-onset retinal degeneration (LORD)

LORD often manifests in a similar way to SFD and is also inherited in an autosomal dominant pattern (mutations in the *C1QTNF5* gene). In early disease stages, reticular pseudodrusen typically occur and atrophy usually develops in later stages (▶ **Fig. 3b**). First symptoms often include reduced dark adaptation and/or reduced contrast sensitivity. CNV development may occur in various locations, including the centre, the edge of atrophy, and the periphery. Non-exudative CNVs have also been reported [14]. Some patients show zonular fibres with an unusually anterior attachment on the anterior lens surface.

Extensive macular atrophy with pseudodrusen (EMAP)

This clinical condition first described in 2009 exhibits pseudodrusen and relatively rapid progression of chorioretinal atrophy occurring mostly in patients in their fifth or sixth decade of life; the atrophy typically extends more vertically than horizontally [15, 16]. Fundoscopy shows pronounced reticular pseudodrusen extending into the mid-periphery. Areas of atrophy usually develop above the fovea before extending more vertically than horizontally. Patients typically show a pronounced reduction in contrast vision and dark adaptation even with visual acuity still unimpaired. Based on FAF findings, some EMAP cases might previously have been classified as "diffuse trickling GA" [17]. Visual acuity decreases significantly once the initial foveal sparing also develops atrophy. Genetic and/or environmental factors likely play a role in the pathophysiology, although this has not yet been proven (▶ **Fig. 3c**).

Pseudoxanthoma elasticum (PXE)

This systemic disease entails increased and early calcification of connective tissue rich in elastin fibres. In the eye, this mainly affects Bruch's membrane with calcification progressing centrifugally from the posterior pole to the periphery [18]. The transition zone between calcified and normal Bruch's membrane may take on a peau d'orange appearance. Many patients with PXE subsequently develop reticular pseudodrusen as well as hypopigmentation and hyperpigmentation that may have a similar appearance to a pattern dystrophy [19]. Areas of chorioretinal atrophy typically develop initially around the optic nerve. Atrophy may progress into the macular region and may become widespread later on. The development of MNV is common and should be treated aggressively with VEGF antagonists [20]. Importantly, fundus changes may also manifest late in mild cases of PXE with clinically relevant changes limited to ocular manifestations [21] (▶ **Fig. 3d**). Other systemic changes include those in the skin giving the disease its name as well as premature calcification in arterial vessels with claudication as the main symptom.

Diseases With Drusen-like Changes

Macular dystrophies

Monogenic macular dystrophies are genetically and phenotypically heterogeneous [22]. Drusen-like alterations may be observed and may depend on the on the genotype and disease stage. Often, these changes are described as flecks. Differentiation from AMD drusen is often achieved with multimodal retinal imaging.

Fleck-like changes in Stargardt's disease may be confused with drusen, especially in mild cases, and therefore late-onset manifestations of retinal dystrophy may be overlooked. Mutations in the *ABCA4* gene are the most common cause for Stargardt's disease (autosomal recessive inheritance, ▶ **Fig. 4a**). Other similar phenotypes may arise from mutations in the *Peripherin 2* gene (*PRPH2*; ▶ **Fig. 4b**) or *Elongation of very long chain fatty acids protein 4* gene (*ELOVL4*) in conditions with autosomal dominant inheritance. Patients with mutations in *the CDHR1* gene may also show fine drusen-like changes (▶ **Fig. 4c**).

Fundus albipuncatus is another monogenic retinal disease that presents with drusen-like changes. This phenotype is associated with mutations in genes with products involved in the visual cycle. Patients typically have reduced dark adaptation since birth, as rhodopsin is recycled at a slower rate (▶ **Fig. 4d**).

Vitelliform lesions have also been observed in monogenic macular dystrophies – including in the elderly. Examples include late-onset Best disease or *IMPG2*-associated maculopathy [23] (▶ **Fig. 5a**).

North Carolina Macular Dystrophy (NCMD)

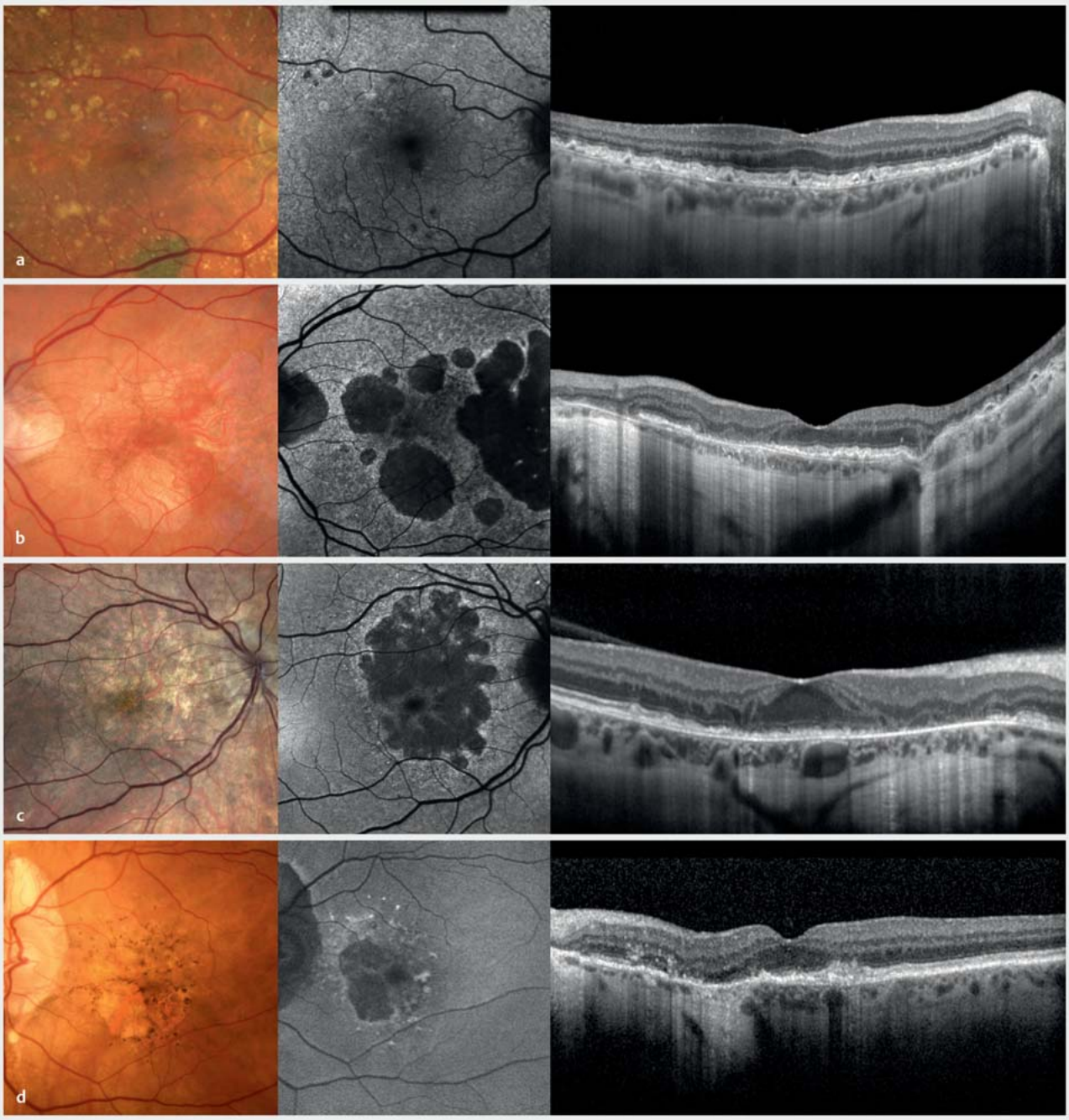
NCMD is mainly a benign and barely progressive congenital disorder of the macular area. Mutations affecting the *PRDM13* gene cause this macular condition. It can be challenging to distinguish between NCMD and AMD, especially in older patients – due to the much more benign disease course and autosomal dominant inheritance, therefore differential diagnosis and counselling is particularly valuable. NCMD can manifest in various forms; whereby small, yellowish, drusen-like changes in the macular area appear to be common (▶ **Fig. 5b**). These drusen are typically finer than most other drusen, can rarely be detected on OCT imaging, and typically show an increased autofluorescence signal [24]. Most NCMD patients show similar drusen-like changes in the periphery. More pronounced findings can present as congenital atrophy in the macular area (▶ **Fig. 5c**), which occasionally also shows a coloboma-like appearance. Occasionally, secondary MNVs may develop.

Benign yellow dot maculopathy (BYDM)

These yellowish dots around the macula were first described as an entity in 2017 [25]. These changes usually have no obvious phenotypic correlate on OCT imaging, whereas autofluorescence examination shows increased autofluorescence (▶ **Fig. 5d**). Patients are usually asymptomatic; functional examinations usually show no impairment. Familial clustering has been observed; at least some of those affected may show dominant inheritance. BYDM and NCMD are occasionally very similar in appearance, but it is unusual for BYDM to show peripheral drusen-like changes.

Primary hyperoxaluria

Primary hyperoxaluria (PH) encompasses a group of autosomal recessive disorders (PH1-PH3) with alteration of the glyoxylate metabolism. Endogenous overproduction of insoluble oxalates mainly leads to kidney disease resulting in kidney failure. However, calcium oxalate crystals occur not only in the kidneys, but may also be found in other organs such as bones, heart muscle, and eyes. Patients with infantile PH1 exhibit severe systemic oxalate



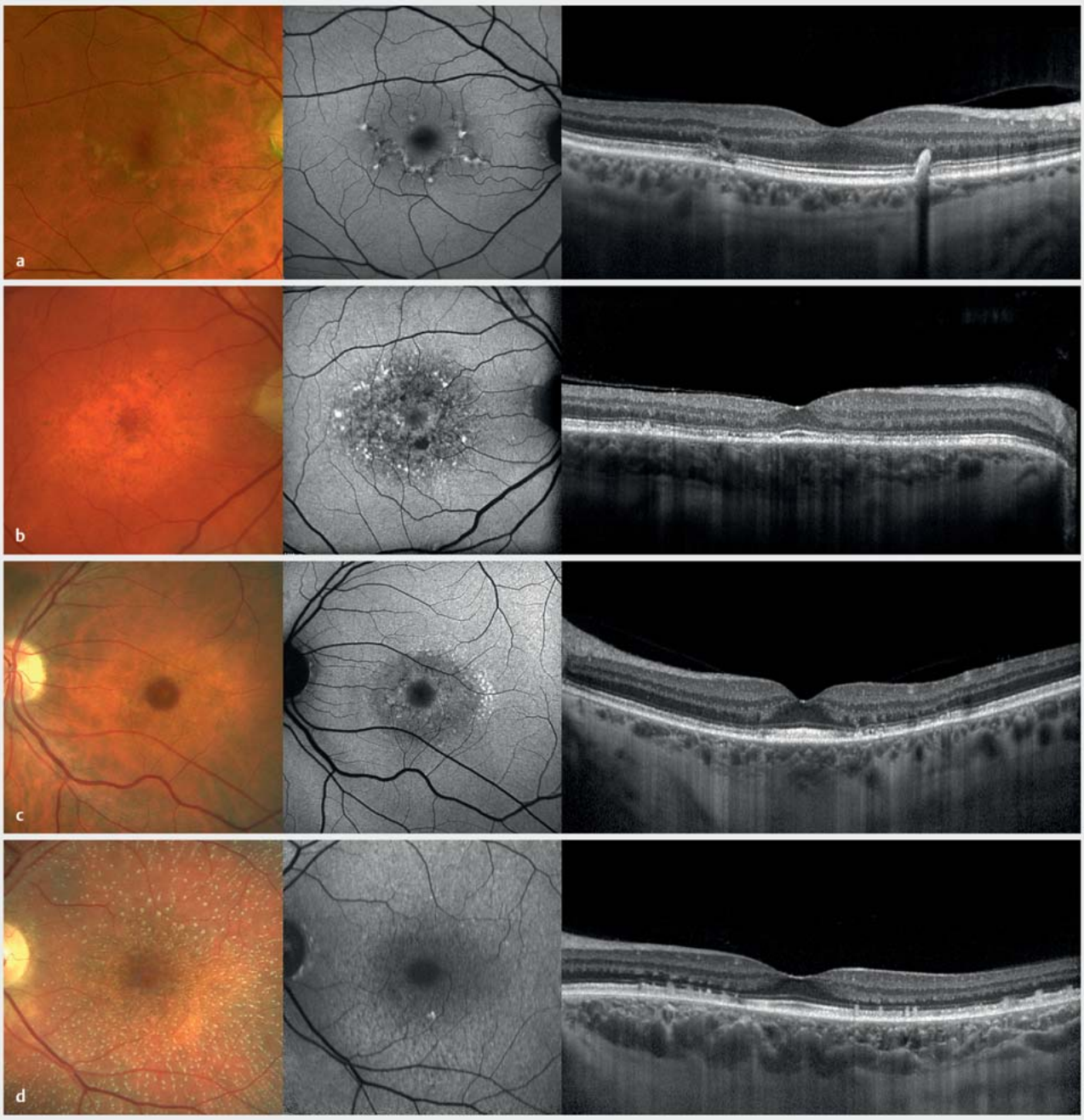
▶ **Fig. 3** Differential diagnoses of age-related macular degeneration – diseases characterised by drusen. Left to right: Fundus photography, fundus autofluorescence, optical coherence tomography (OCT). **a** Sorsby Fundus Dystrophy. **b** Late-onset retinal degeneration. **c** Extensive Macular Atrophy with Pseudodrusen (images by Dr. Francesco Romano). **d** Pseudoxanthoma elasticum. Age of patients (in years): **a:** 64; **b:** 70; **c:** 53; **d:** 82.

deposits that may lead to severe vision loss even at a young age. Patients with non-infantile PH1 may show small drusen-like retinal changes appearing as hyperreflective subretinal lesions on OCT and as changes with increased autofluorescence (▶ **Fig. 5 e**). Visual function is usually not significantly impaired [26, 27]; only minimal subretinal deposits have been reported in patients with PH3 [28].

Other Monogenic Diseases

Macular dystrophies and cone dystrophies

Apart from hereditary retinal diseases as described above, macular dystrophies may also be misdiagnosed as AMD even without drusen-like changes, especially in the atrophic or late form/geo-

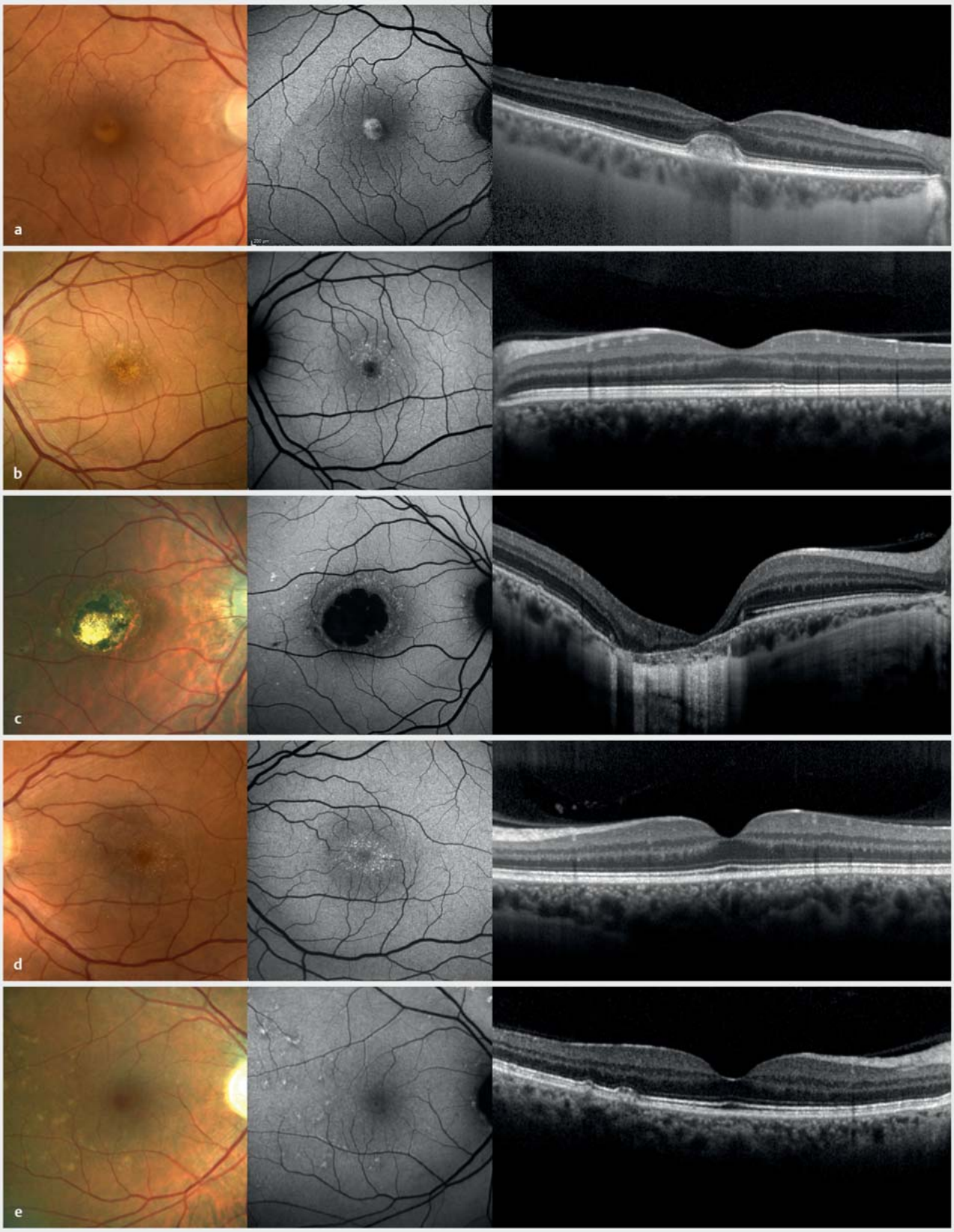


▶ **Fig. 4** Differential diagnoses of age-related macular degeneration – diseases characterised by drusen-like changes. Left to right: Fundus photography, fundus autofluorescence, optical coherence tomography (OCT). Patients with mutations in *ABCA4* (**a**), *PRPH2* (**b**), *CDHR1* (**c**), and *RDH5* (**d**). Age of patients (in years): **a:** 63; **b:** 69; **c:** 48; **d:** 49.

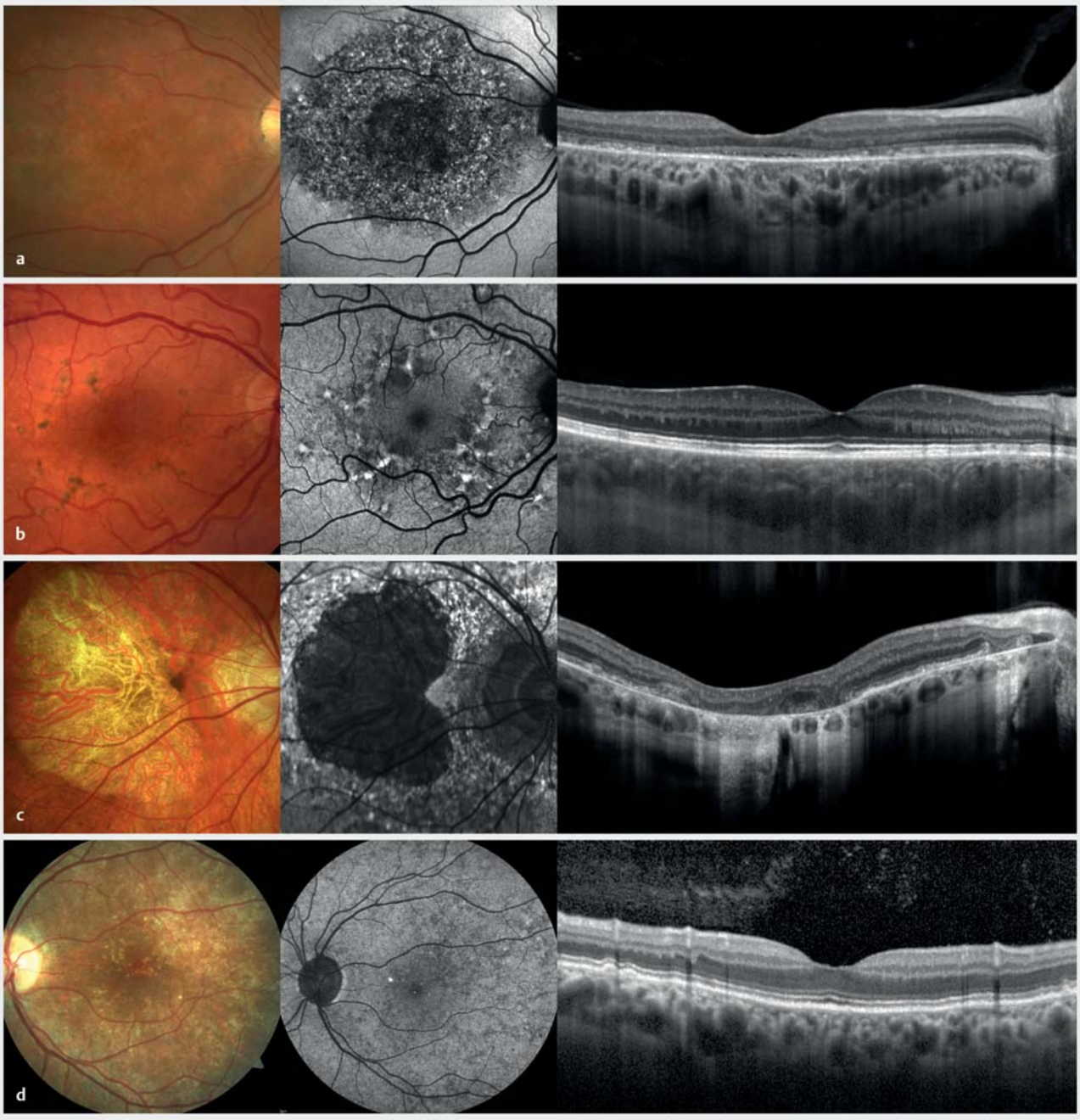
graphic atrophy [29]. A diagnosis of macular dystrophy is often delayed, especially when manifestations arise at an older age. In some genetic conditions such retinopathies associated with specific mutations in the *ABCA4*, *PRPH2* and *CDHR1* genes, initial symptoms may frequently occur after the age of 50. (▶ **Fig. 6** and **7**).

Mitochondrial retinopathy

Mitochondrial retinopathies show a characteristic retinal phenotype that may allow the diagnosis of mitochondrial disease, both in patients with mild systemic disease and patients with severe multisystem disease of unknown cause [30]. Early and accurate diagnosis can be crucial to identify (treatable) systemic manifestations, to adjust lifestyle or to avoid medication that impairs mito-

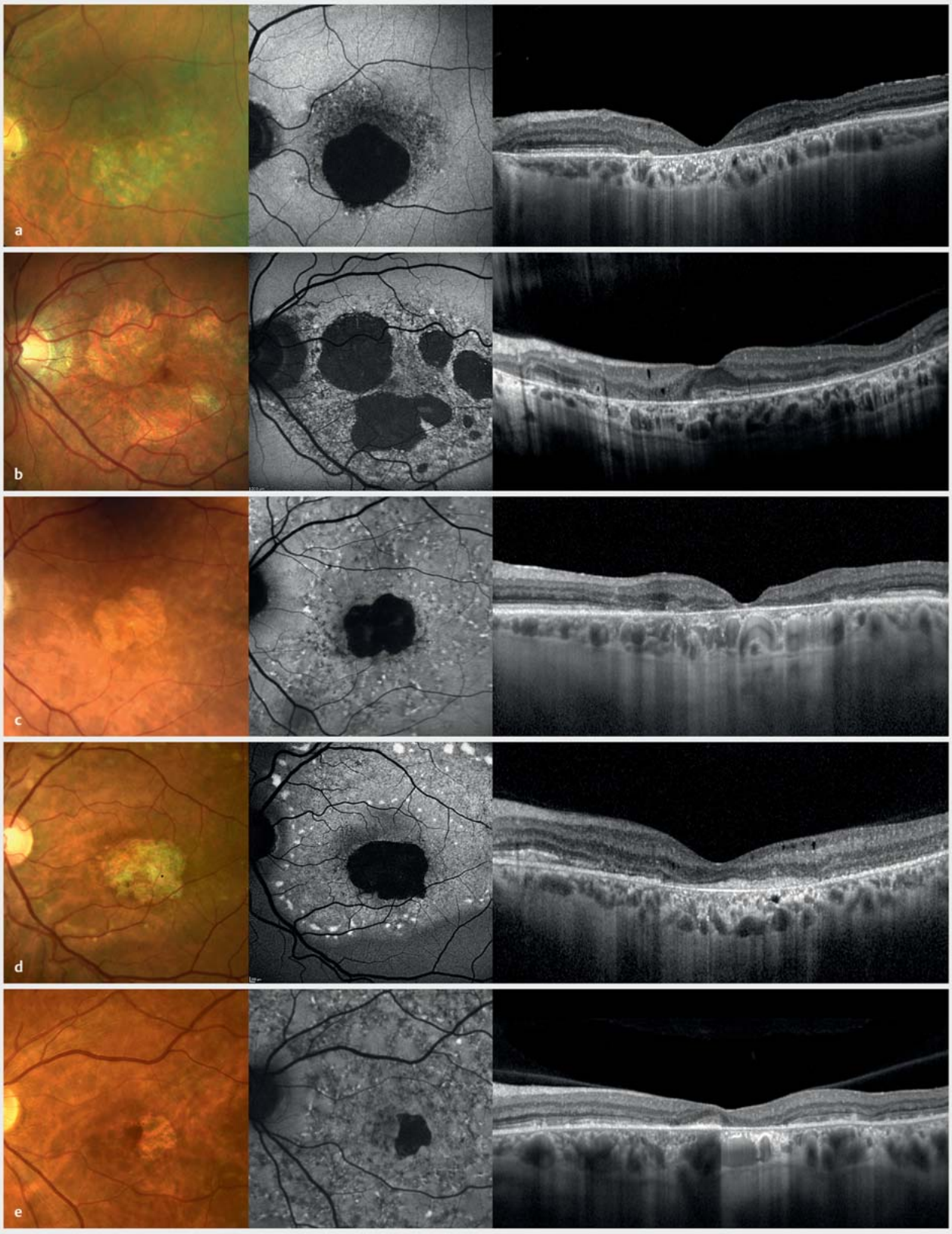


▶ **Fig. 5** Differential diagnoses of age-related macular degeneration – diseases characterised by drusen-like changes. Left to right: Fundus photography, fundus autofluorescence, optical coherence tomography (OCT). **a** *IMPG2* -associated Maculopathy. **b, c** North Carolina Macular Dystrophy. **d** Benign Yellow Dot Maculopathy. **e** Primary Hyperoxaluria type 1. Age of patients (in years): **a:** 70; **b:** 44; **c**: 26; **d:** 38; **e:** 59.



▶ **Fig. 6** Differential diagnoses of age-related macular degeneration – other monogenic diseases. Left to right: Fundus photography, fundus autofluorescence, optical coherence tomography (OCT). **a** *PRPH2*-associated maculopathy. **b**, **c** Mitochondrial retinopathy. **d** Choroideraemia carrier. Age of patients (in years): **a:** 53; **b:** 51; **c:** 53; **d:** 45.

chondrial function. Retinal changes can be divided into three subtypes with characteristic phenotypes. Patients with type 1 mitochondrial retinopathy usually show mild focal pigment changes in the retina. Type 2 mitochondrial retinopathy shows a spectrum of retinal changes ranging from subtle pigmentary changes to yellowish or lightly pigmented subretinal deposits to chorioretinal atrophy with or without foveal involvement (▶ **Fig. 6b**, **c**). Type 3 features extensive granular pigment changes with or without chorioretinal atrophy. Many patients with mitochondrial retinopathy only have mild symptoms and retain good visual acuity due to the relative sparing of the fovea despite pronounced retinal changes, although poor lighting conditions often cause visual disturbances.



▶ **Fig. 7** Differential diagnoses of age-related macular degeneration – other monogenic diseases. Left to right: Fundus photography, fundus autofluorescence, optical coherence tomography (OCT). Patients with mutations in *CDHR1* (**a**), *PRPH2* (**b**, **c**) , *BEST1* (autosomal recessive) (**d**), and *ABCA4* (**e**). Age of patients (in years): **a:** 81; **b:** 52; **c:** 78, **d:** 48; **e:** 59.

Choroideraemia carriers

Chorioideremia is an X-linked inherited disorder leading to blindness in males, usually in middle age, due to progressive chorioretinal atrophy originating in the mid-periphery. Symptoms are similar to those of retinitis pigmentosa. Female carriers of a mutation in the *CHM* gene usually show fine-spotted RPE changes and occasionally drusen-like deposits (▶ **Fig. 6 d**) [31, 32]. Limited visual impairment such as reduced vision or impaired dark adaptation may also exist depending on the severity.

A similar phenotype may be observed in patients with X-linked Danon disease [33]. Even though the disease is very rare, the ophthalmic findings may be indicative. Young male patients with such a phenotype should be referred for a cardiological assessment, as severe hypertrophic cardiomyopathy is usually found.

Other Macular Diseases

A wide variety of other macular diseases can exhibit characteristics similar to AMD. Changes should therefore be seen in the context of the patient's overall clinical picture to make correct diagnosis. Vitelliform macular lesions for example may occur in AMD, but also in retinal dystrophies, chronic vitreomacular traction, and central serous chorioretinopathy (CSC) to name just three. Subretinal fluid is not solely seen in AMD, but also in a variety of other diseases such as CSC or PXE and does not require the same treatment without evidence of MNV. Identifying an active MNV can be challenging in some cases, such as in patients with myopic retinal changes. Some examples of other macular diseases are described below.

Macular telangiectasia type 2 (MacTel)

This primary neurodegenerative macular disease often shows only mild changes, but may lead to photoreceptor atrophy within the macula [34]. The disease usually manifests in an oval area centred on the fovea [35]. Initial changes typically occur within this "MacTel" region temporal to the foveal centre, and the most pronounced changes remain temporal even in advanced stages. Other characteristic findings include the vascular changes that give the disease its name, as well as hyperpigmentation (▶ **Fig. 8 a**). Neovascular membranes are observed less frequently; these usually develop from the retinal vascular network and usually exhibit only minimal exudation and progression. Neovascularisation may remain under observation or undergo minimal treatment using VEGF antagonists if symptoms occur as more frequent injections may have negative long-term effects [36].

Fundus autofluorescence and fundus reflectance imaging with blue light are especially helpful in diagnosis, in addition to OCT. Typical findings include absence of macular pigment and increased blue light reflectivity in the MacTel region [37, 38].

Dome-shaped or ridge-shaped macula

This anatomical variant of the posterior pole of the eye was first described in 2008 [39]. The macular protrusions that give the disease its name are frequently observed in high myopia. OCT images in horizontal and vertical directions are essential for diagnosis, especially in ridge-shaped macula. Typical macular findings entail changes in pigmentation and irregular RPE bands. Subretinal fluid may be found without presence of a MNV; visual acuity usually remains relatively stable for a long time even though subretinal fluid does not respond to therapeutic intervention (which is therefore unnecessary) (▶ **Fig. 8 b**).

Macular degeneration as medication side effects

A comprehensive general medical history, including a detailed medication history, allows the identification of retinal changes caused by side effects of medication which may mimic a primary retinal disease. Deferoxamine (▶ **Fig. 8 c**), hydroxychloroquine (▶ **Fig. 8 d**), and pentosan polysulfate are examples of such medication. If a medication associated retinopathy occurs, the causative medication should – if possible – be discontinued.

Congenital rubella retinopathy

Congenital rubella retinopathy features fine-spotted macular pigment changes, with variable extension into the periphery [40]. OCT examination reveals hyperreflective material that may be confused with drusen. Autofluorescence examination usually shows a distinct granular pattern, asymmetry at the fundus and between the eyes is not uncommon (▶ **Fig. 8 e**). These changes are usually asymptomatic; hence, the diagnosis may sometimes be established at advanced age. The clinical findings together with the history of a maternal rubella infection during pregnancy enable diagnosis – further diagnostic confirmation through diagnostic tests is not available. Patients with rubella retinopathy may also have sensorineural hearing loss and other manifestations of rubella embryofetopathy.

Inflammatory and post-inflammatory changes

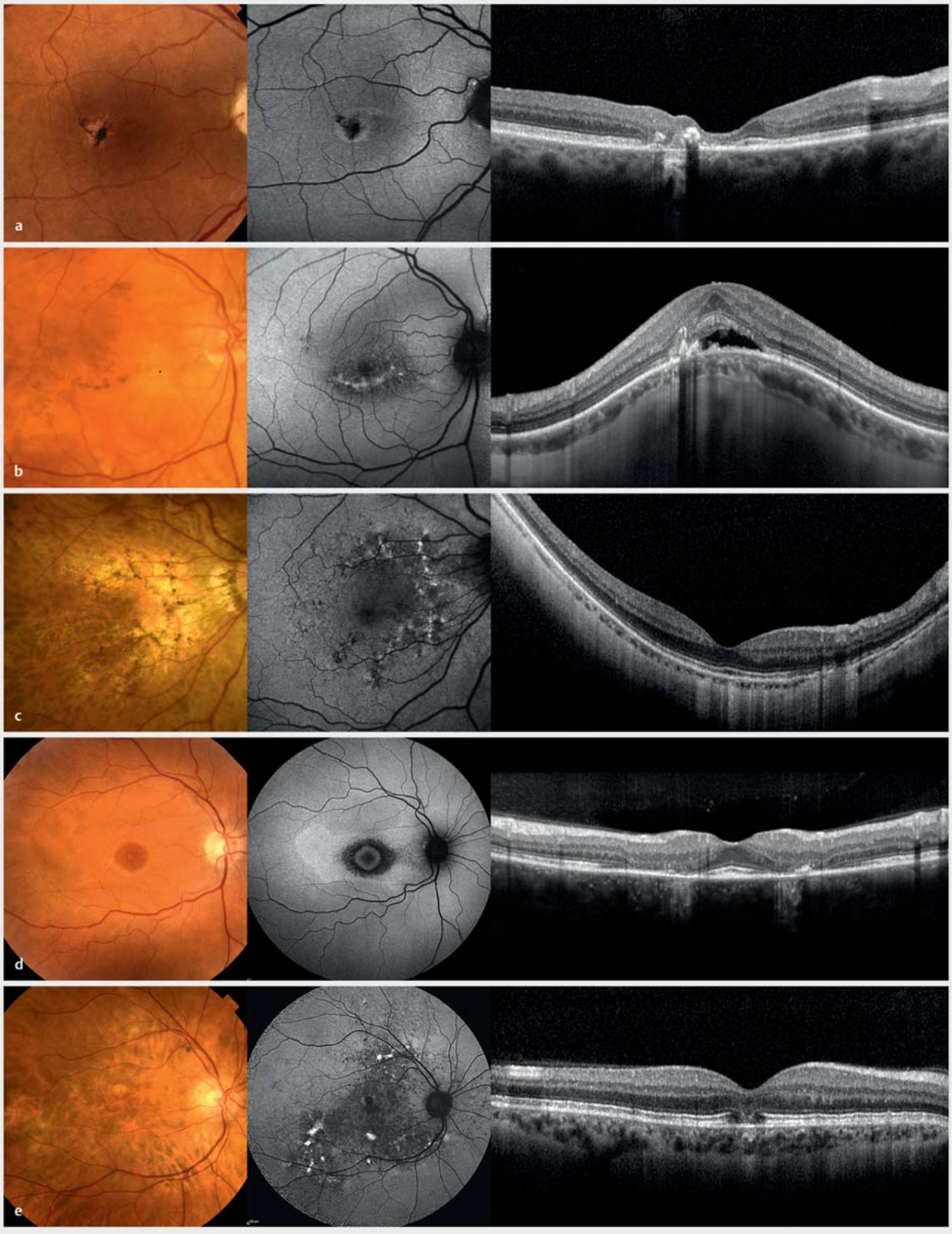
Inflammatory and post-inflammatory diseases should also be considered as differential diagnoses in presence of certain clinical findings. Risk factors such as female gender, younger age, and myopia may help distinguish punctate inner choroidopathy (PIC) from other forms of retinopathy. Further investigation is always advised on suspicion of posterior uveitis or retinitis in syphilis.

Geographic Atrophy

The development of novel therapies for patients with AMD and geographic atrophy have made it increasingly important to establish the correct diagnosis in this final stage of many macular diseases. Most of the diseases described above lead ultimately to a phenotpye comparable to GA with photoreceptor and retinal pigment epithelium atrophy.

Differential diagnoses should be especially considered in younger patients with atrophy of the outer retina, absence of adjacent drusen or (pronounced) symmetry of the atrophy. Examination at a centre specialised in rare retinal diseases with molecular genetic testing may be beneficial on suspicion of retinal dystrophy. However, the clinical diagnosis cannot be supported by molecular genetics in all patients with retinal dystrophies – a negative result from comprehensive molecular genetic diagnostics merely indicates that no mutations explaining the clinical findings were found [29].

Multimodal retinal imaging plays an important role in differential diagnosis, as it may reveal changes that cannot be detected by



▶ **Fig. 8** Differential diagnoses for age-related macular degeneration. Left to right: Fundus photography, fundus autofluorescence (FAF), optical coherence tomography (OCT). **a** Type 2 macular telangiectasia (MacTel). **b** Dome-shaped or ridge-shaped macula. **c** Deferoxamine retinopathy (with high myopia as a secondary finding). **d** Hydroxychloroquine retinopathy. **e** Congenital rubella retinopathy. Age of patients (in years): **a:** 87; **b:** 70; **c:** 55; **d:** 50; **e:** 54.

fundoscopic examination. For example, OCT may be more effective at detecting drusen surrounding the atrophic area than fundoscopic examination, whereas fundus autofluorescence (FAF) may provide information on both diagnosis and spread of the disease. FAF may also reveal characteristic changes when fundoscopy fails to show any obvious manifestations. Regarding differential diagnosis, areas with increased autofluorescence may indicate *ABCA4*-associated retinopathy, or a vitelliform lesion with increased autofluorescence may indicate mutations in the *IMPG2* gene or autosomal dominant Best disease. Combining different modalities is most useful, sometimes allowing a clear diagnosis without requiring further functional and/or molecular genetic diagnostics.

Summary

There are a variety of clinical conditions that can resemble AMD but may differ in terms of prognosis, heredity, monitoring and treatment requirements. Clinical examination alone is often not sufficient for achieving a specific diagnosis – a detailed medical history, multimodal imaging and additional molecular genetic testing may be required.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

[1] Finger RP, Fimmers R, Holz FG et al. Prevalence and causes of registered blindness in the largest federal state of Germany. Br J Ophthalmol 2011; 95: 1061–1067

[2] Li JQ, Welchowski T, Schmid M et al. Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. Br J Ophthalmol 2020; 104: 1077–1084

[3] Pondorfer SG, Terheyden JH, Heinemann M et al. Association of Vision-related Quality of Life with Visual Function in Age-Related Macular Degeneration. Sci Rep 2019; 9: 15326

[4] Taylor DJ, Jones L, Binns AM et al. ‚You've got dry macular degeneration, end of story': a qualitative study into the experience of living with non-neovascular age-related macular degeneration. Eye (Lond) 2020; 34: 461–473

[5] Russell SR, Mullins RF, Schneider BL et al. Location, substructure, and composition of basal laminar drusen compared with drusen associated with aging and age-related macular degeneration. Am J Ophthalmol 2000; 129: 205–214

[6] Boon CJ, van de Ven JP, Hoyng CB et al. Cuticular drusen: stars in the sky. Prog Retin Eye Res 2013; 37: 90–113

[7] Finger RP, Charbel Issa P, Kellner U et al. Spectral domain optical coherence tomography in adult-onset vitelliform macular dystrophy with cuticular drusen. Retina 2010; 30: 1455–1464

[8] Castro-Navarro V, Behar-Cohen F, Chang W et al. Pachychoroid: current concepts on clinical features and pathogenesis. Graefes Arch Clin Exp Ophthalmol 2021; 259: 1385–1400

[9] Stone EM, Lotery AJ, Munier FL et al. A single EFEMP1 mutation associated with both Malattia Leventinese and Doyne honeycomb retinal dystrophy. Nat Genet 1999; 22: 199–202

[10] Michaelides M, Jenkins SA, Brantley MA jr. et al. Maculopathy due to the R345 W substitution in fibulin-3: distinct clinical features, disease variability, and extent of retinal dysfunction. Invest Ophthalmol Vis Sci 2006; 47: 3085–3097

[11] Gliem M, Muller PL, Mangold E et al. Sorsby Fundus Dystrophy: Novel Mutations, Novel Phenotypic Characteristics, and Treatment Outcomes. Invest Ophthalmol Vis Sci 2015; 56: 2664–2676

[12] Gliem M, Müller PL, Mangold E et al. Reticular Pseudodrusen in Sorsby Fundus Dystrophy. Ophthalmology 2015; 122: 1555–1562

[13] Meunier I, Bocquet B, Labesse G et al. A new autosomal dominant eye and lung syndrome linked to mutations in TIMP3 gene. Sci Rep 2016; 6: 32544

[14] Keenan TDL, Vanderford EK, de Silva T et al. Massive Advancing Nonexudative Type 1 Choroidal Neovascularization in CTRP5 Late-Onset Retinal Degeneration: Longitudinal Findings on Multimodal Imaging and Implications for Age-Related Macular Degeneration. Retina 2021; 41: 2236–2245

[15] Hamel CP, Meunier I, Arndt C et al. Extensive macular atrophy with pseudodrusen-like appearance: a new clinical entity. Am J Ophthalmol 2009; 147: 609–620

[16] Romano F, Cozzi M, Monteduro D et al. Natural Course and Classification of Extensive Macular Atrophy with Pseudodrusen-Like Appearance. Retina 2023; 43: 402–411

[17] Holz FG, Bindewald-Wittich A, Fleckenstein M et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol 2007; 143: 463–472

[18] Charbel Issa P, Finger RP, Götting C et al. Centrifugal fundus abnormalities in pseudoxanthoma elasticum. Ophthalmology 2010; 117: 1406–1414

[19] Gliem M, Hendig D, Finger RP et al. Reticular pseudodrusen associated with a diseased bruch membrane in pseudoxanthoma elasticum. JAMA Ophthalmol 2015; 133: 581–588

[20] Gliem M, Finger RP, Fimmers R et al. Treatment of choroidal neovascularization due to angioid streaks: a comprehensive review. Retina 2013; 33: 1300–1314

[21] Charbel Issa P, Tysoe C, Caswell R. Late-Onset Pseudoxanthoma Elasticum Associated with a Hypomorphic ABCC6 Variant. Am J Ophthalmol 2020; 218: 255–260

[22] Birtel J, Eisenberger T, Gliem M et al. Clinical and genetic characteristics of 251 consecutive patients with macular and cone/cone-rod dystrophy. Sci Rep 2018; 8: 4824

[23] Birtel J, Caswell R, De Silva SR et al. IMPG2-Related Maculopathy. Am J Ophthalmol 2023; 258: 32–42

[24] Birtel J, Gliem M, Herrmann P et al. North Carolina macular dystrophy shows a particular drusen phenotype and atrophy progression. Br J Ophthalmol 2022; 106: 1269–1273

[25] Dev Borman A, Rachitskaya A, Suzani M et al. Benign Yellow Dot Maculopathy: A New Macular Phenotype. Ophthalmology 2017; 124: 1004–1013

[26] Birtel J, Herrmann P, Garrelfs SF et al. The Ocular Phenotype in Primary Hyperoxaluria Type 1. Am J Ophthalmol 2019; 206: 184–191

[27] Birtel J, Charbel Issa P, Herrmann P et al. Examination of the eye and retinal alterations in primary hyperoxaluria type 1. Nephrol Dial Transplant 2022; 37: 255–257

[28] Birtel J, Diederen RM, Herrmann P et al. The retinal phenotype in primary hyperoxaluria type 2 and 3. Pediatr Nephrol 2023; 38: 1485–1490

[29] Birtel J, Yusuf IH, Priglinger C et al. Diagnosis of Inherited Retinal Diseases. Klin Monbl Augenheilkd 2021; 238: 249–259

[30] Birtel J, von Landenberg C, Gliem M et al. Mitochondrial Retinopathy. Ophthalmol Retina 2022; 6: 65–79

[31] Gocuk SA, Jolly JK, Edwards TL et al. Female carriers of X-linked inherited retinal diseases – Genetics, diagnosis, and potential therapies. Prog Retin Eye Res 2023; 96: 101190

[32] Murro V, Mucciolo DP, Passerini I et al. Retinal dystrophy and subretinal drusenoid deposits in female choroideremia carriers. Graefes Arch Clin Exp Ophthalmol 2017; 255: 2099–2111

[33] Kousal B, Majer F, Vlaskova H et al. Pigmentary retinopathy can indicate the presence of pathogenic LAMP2 variants even in somatic mosaic carriers with no additional signs of Danon disease. Acta Ophthalmol 2021; 99: 61–68

[34] Charbel Issa P, Gillies MC, Chew EY et al. Macular telangiectasia type 2. Prog Retin Eye Res 2013; 34: 49–77

[35] Heeren TFC, Chew EY, Clemons T et al. Macular Telangiectasia Type 2: Visual Acuity, Disease End Stage, and the MacTel Area: MacTel Project Report Number 8. Ophthalmology 2020; 127: 1539–1548

[36] Kupitz EH, Heeren TF, Holz FG et al. Poor Long-Term Outcome of Anti-Vascular Endothelial Growth Factor Therapy in Nonproliferative Macular Telangiectasia Type 2. Retina 2015; 35: 2619–2626

[37] Pauleikhoff L, Heeren TFC, Gliem M et al. Fundus Autofluorescence Imaging in Macular Telangiectasia Type 2: MacTel Study Report Number 9. Am J Ophthalmol 2021; 228: 27–34

[38] Charbel Issa P, Berendschot TT, Staurenghi G et al. Confocal blue reflectance imaging in type 2 idiopathic macular telangiectasia. Invest Ophthalmol Vis Sci 2008; 49: 1172–1177

[39] Gaucher D, Erginay A, Lecleire-Collet A et al. Dome-shaped macula in eyes with myopic posterior staphyloma. Am J Ophthalmol 2008; 145: 909–914

[40] Bukowska DM, Wan SL, Chew AL et al. Fundus Autofluorescence in Rubella Retiniopathy: Correlation With Photoreceptor Structure and Function. Retina 2017; 37: 124–134