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RESEARCH ARTICLE

Optic disc drusen: new hypotheses on systemic calcification

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ABSTRACT

Optic disc drusen (ODD) are acellular calcified deposits within the optic nerve head. They arise early in life, usually remain asymptomatic with a benign prognosis, and they are most often clinically relevant as they can be mistaken for papilloedema, can result in asymptomatic optic nerve thinning resembling glaucoma, or can have complications such as anterior ischaemic optic neuropathy with sudden loss of vision. There is still a lot of uncertainty about the pathogenesis of ODD, and prognostic factors for vision loss in the long term. The strongest association of ODD is with pseudoxanthoma elasticum, a condition of systemic ectopic calcification. Understanding the shared biochemical pathways underlying pseudoxanthoma elasticum and other conditions with the same phenotype, highlights pyrophosphate as an important factor in ectopic calcification and a potential therapy.

Introduction

Optic disc drusen (ODD) are acellular calcified concretions in the optic nerve head, which are seldom symptomatic[1]. The clinical presentation can vary widely, so ODD may remain asymptomatic and undetected for most people but can cause substantial vision loss for others. The underlying causes and contributing factors are poorly understood and there is no treatment for ODD. Here we aim to review the essential clinical features of ODD, and how systemic associations shed light on underlying pathogenesis. This highlights the role of pyrophosphate deficiency in many inherited disorders of ectopic calcification, and the role of pyrophosphate and related molecules as potential therapy of ectopic calcification disorders such as ODD.

Clinical features and prognosis

The clinical presentation of ODD is highly varied. In some patients they give the impression of optic disc oedema (pseudopapilloedema), particularly in younger patients with headaches, which can result in anxiety and excessive investigation[2]. In other patients with ODD, sudden monocular vision loss can occur from anterior ischaemic optic neuropathy (AION), and ODD are thought to be an important risk factor for AION in younger healthy patients[3-6]. In most cases, ODD are diagnosed after incidental asymptomatic observations such as peripapillary haemorrhages or abnormal optic disc appearance or thinning of the retinal nerve fibre layer (RNFL) on an optical coherence tomography (OCT) scan. Indeed, the majority of ODD are undiagnosed throughout life, understood from the fact that the post-mortem histological prevalence is several times greater than the clinical prevalence[7,8].

The prevalence of ODD depends very much on how they are detected, defined, and diagnosed. Using clinical examination, perhaps retinal photography, the prevalence is low, in the order of 0.2%-0.5% in both adults and children[2,9,10]. Cadaver studies, with histological examination of many otherwise normal eyes, showed a higher prevalence around 2%[8]. Indeed thinner sections result in more sensitive examination and detection of more numerous, smaller and deeper drusen[11].

Various imaging modalities can detect ODD: fundus autofluorescence can detect superficial or exposed ODD, ultrasound and CT can detect larger calcified ODD, and fluorescein angiography can be useful to differentiate true optic disc oedema (leakage) from buried ODD (staining)[12-15]. The OCT has now emerged as the most sensitive method to detect ODD, and published guidelines for enhanced depth imaging (EDI, or swept-source OCT) to improve detection of deeper drusen were a landmark in this condition[14-18]. With EDI OCT a higher prevalence of 1.0-2.3% was observed, close to the post-mortem histological prevalence, and hyper-reflective bands (though to be very small subclinical drusen or precursors to drusen) were present in another 2-12%[10,19,20]. Thus, small subclinical ODD are a very common finding in normal eyes, detectable only with high resolution targeted OCT imaging.

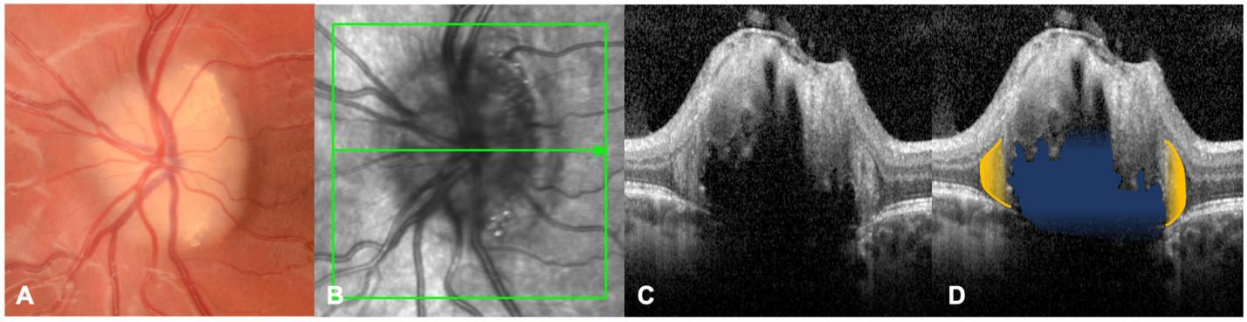

Figure 1. Colour photograph (A), infrared laser ophthalmoscopy image (B) and an enhanced depth imaging (EDI) optical coherence tomography (OCT) cross section of an optic nerve head (C and D), demonstrating optic disc drusen (ODD), with large buried drusen (coloured blue in D). The typical appearance is usually a hypo-reflective core and hyper-reflective margins and are located above the lamina cribosa. Also visible are peripapillary hyper-reflective ovoid mass-like structures (PHOMS, coloured yellow in D), which are commonly present with ODD, but also occur with other conditions including tilted discs, or true disc oedema.

Most ODD are bilateral, and a majority have some thinning of the retinal nerve fibre layer (RNFL) and corresponding visual field defect[21,22]. The long-term prognosis for these eyes is of greatest clinical relevance. Cases are reported with growth of drusen and loss of RNFL within the first few decades of life[20,23-25], but then ODD are remarkably stable throughout adulthood[26-28]. The rate of visual field progression in adults is probably faster than the rate of normal age-related deterioration[27,29,30], but cases of severe visual loss are rare and thought to be complicated by AION[31,32]. The prevalence of ODD is not much different in children and adults[2,10], also supporting the stability of this condition in adulthood.

It remains debated whether modifiable factors, such as intraocular pressure, affect the rate of visual field loss in adulthood[22,30,33,34].

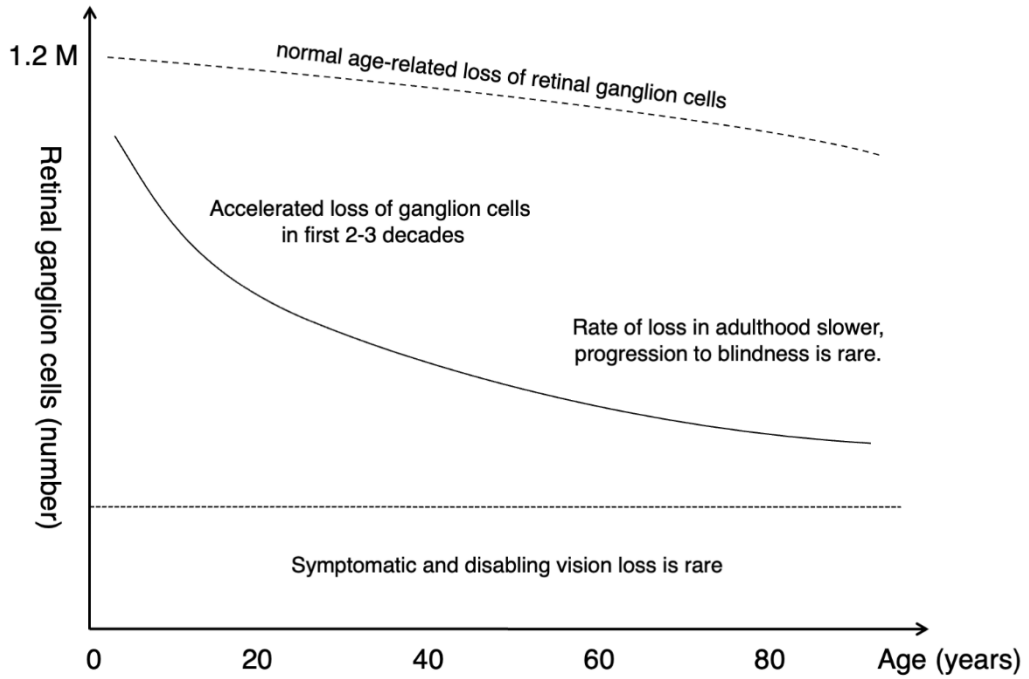

Figure 2. Simplified graph showing the imagined age-related loss of retinal ganglion cells (RGC) over a lifetime. Normal eyes (dotted line) are contrasted with the understanding that eyes with ODD (solid line) often have accelerated loss of RGC in the first three decades of life, followed by relative stability in adulthood. Progressive loss of RGC to severe or symptomatic vision loss is rare.

Pathogenesis

The pathogenesis of ODD is not well understood but several observations must be considered when proposing a theory of their cause[35]. They are common, bilateral, often subclinical, most common in the nasal part of the disc, and always present just anterior to lamina cribrosa. They are present early in life and may grow and progress during the first few decades. ODD are acellular concretions, comprised of calcium phosphate (and a range of other molecules such as amino acids, mucopolysaccharides and glycoproteins)[36,37], and since the earliest descriptions authors recognised histological similarities between Bruch's membrane and ODD[38].

One human eye with ODD has been subject to transmission electron microscopy, and the findings have been extrapolated to generate theories of pathogenesis[11]. Heavily calcified mitochondria were found, including in the extracellular spaces of the optic nerve head, which is an unusual pathological finding (because extracellular mitochondria usually elicit an inflammatory reaction and are rapidly phagocytosed). Dysfunctional mitochondria can become calcified in this way in a range of physiological and pathological situations[39], and their accumulation in the optic nerve head may represent dysfunction of normal axonal transport or dysfunction of the unusual transcellular mitophagy process that is observed in the optic nerve head (in which astrocytes remove expired mitochondria from retinal ganglion cell axons)[40,41].

Pseudoxanthoma elasticum

In considering the pathogenesis of ODD, systemic, and genetic associations are useful guides. The most established associated condition with ODD is pseudoxanthoma elasticum (PXE)[42], a rare sporadic or inherited condition with prevalence around 1:50,000[43,44]. Systemic features of PXE include progressive ectopic calcification of elastic and collagenous connective tissues, resulting in papules and plaques in skin folds, damage to blood vessels causing peripheral arterial occlusive disease and stroke, and kidney stones. The characteristic ophthalmic findings of PXE are angioid streaks and peau d'orange pigment stippling in the fundus, and ODD are much more common than in the general population (9-25%)[45,46]. These ocular features are an ectopic calcification phenotype, and the most vision threatening complications of choroidal neovascularisation and choroidal rupture represent downstream complications of a calcified and brittle Bruch membrane. It is possible to measure increased OCT reflectivity from Bruch membrane as a marker of this increased calcification[47].

The genetic cause of PXE is dysfunction of the ATP binding cassette subfamily C member 6 (ABCC6) gene product[48,49]. This transmembrane protein is found mainly in hepatocytes and renal proximal tubules and facilitates the cellular export adenosine triphosphate (ATP) from the cytoplasm into the extracellular space (Figure 3). Hypothesised functional roles of ABCC6 include the regulation of systemic calcification via pyrophosphate circulation, modulation of fibroblast behaviour and activity, or other local effects in the liver as a regulator of local extracellular ATP levels[50]. On the cell surface, the enzyme ectonucleotide pyrophosphatase/phosphodiesterase 1 (NPP1) converts ATP into adenosine monophosphate and pyrophosphate (AMP + PP_i), while the enzyme

ectonucleoside triphosphate diphosphohydrolase 1 (NTPD1) converts ATP into adenosine diphosphate with inorganic phosphate (ADP + P_i). It seems the liver cell export of ATP, and the balance of P_i and PP_i that results, is the key factor in explaining the increased calcification of PXE (discussed more below). The *Abcc6*$^{-/-}$ mice are a good model of PXE, with a similar phenotype including age-related dystrophic mineralisation of skin, kidneys, blood vessels and Bruch's membrane[51-53].

The effect of PXE on bone health is an area of current interest, as *Abcc6*$^{-/-}$ mice were found to have loss of trabecular bone when relatively elderly (2 years)[54,55], but bone loss was not found in 96 PXE non-elderly adult patients[56].

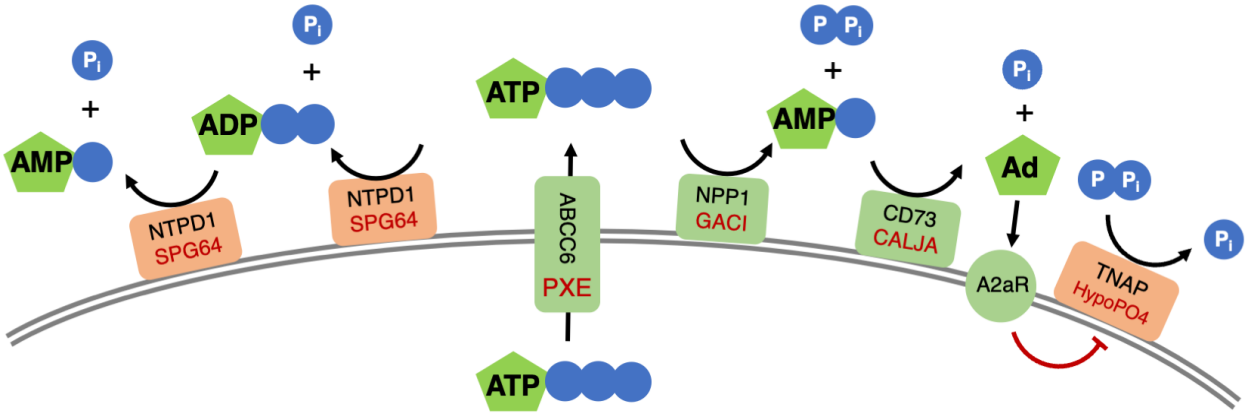

Figure 3. The balance of promotors and inhibitors of calcification on the hepatocyte cell membrane. Proteins that support serum pyrophosphate (PP_i) and inhibit ectopic calcification are shown in green, while proteins that reduce PP_i levels and promote calcification are shown in orange. The ABCC6 transmembrane protein facilitates efflux of adenosine triphosphate (ATP). Extracellular ATP is either converted to adenosine diphosphate (ADP) and inorganic phosphate (P_i) by ectonucleoside triphosphate diphosphohydrolase 1 (NTPD1) or converted to adenosine monophosphate (AMP) and PP_i by ectonucleotide pyrophosphatase/phosphodiesterase 1 (NPP1). Adenosine supports PP_i levels by inhibiting tissue non-specific alkaline phosphatase (TNAP). Diseases associated with dysfunction of each protein are shown in red: PXE, pseudoxanthoma elasticum; GACI, generalised arterial calcification in infancy; CALJA, calcification of joints and arteries; HypoPO4, hypophosphatasia; SPG64, spastic paraplegia type 64. This figure is adapted from multiple similar diagrams in references, including:[48,59,83]

The balance of inhibitors and promotors determine calcification

Hard, mineralised tissues of the body contain large complex crystals of calcium phosphate in the form known as hydroxyapatite (HA, which is $Ca_{10}(PO_4)_6(OH)_2$). While calcium and phosphate are close to saturation in most extracellular fluid, the association of calcium and P_i ions in the correct arrangement is a slow process, affected by other minerals such as magnesium and inhibitors such as PP_i. The formation of HA crystals is greatly facilitated by the process of nucleation where initiation of a crystal on a particle or surface acts as a seed to allow growth of HA crystals.[57] Thus both physiologic and dystrophic calcification firstly involve the association of free calcium ions with extracellular matrix proteins (predominantly elastin or collagen fibres), calcium which then combines with P_i into various chemical intermediate configurations and eventually to HA[58,59]. These processes are not greatly affected by local enzyme or cellular activity, and regulation of calcification relies on relative concentrations of promotors (calcium, P_i) and inhibitors (PP_i and adenosine)[48].

Pyrophosphate, an elusive metabolite

Pyrophosphate (PP_i) is understood to be the circulating factor that explains why reduced ABCC6 expression in the liver increases dystrophic calcification[48,60]. The *Abcc6-/-* mice had no abnormalities of serum calcium, phosphate, sodium, chloride or magnesium (although there was some reduction in plasma high density lipoproteins and increased creatinine)[61], and human liver cell culture demonstrated that ATP release from ABCC6 is the main source of serum PP_i[62,50,63]. Pyrophosphate is a potent inhibitor of HA formation, through direct competitive antagonism against inorganic phosphate on calcium ions, therefore inhibiting the formation of HA[64].

As shown in figure 3, serum PP_i levels relate to the activity of several enzymes in the extracellular space of the liver. Proteins shown in green facilitate the extracellular concentration of PP_i: ABCC6 and NPP1 lead to extracellular PP_i formation, while CD73 and the adenosine receptor A2aR reduce breakdown of PP_i by tissue non-specific alkaline phosphatase (TNAP). Thus, genetic disease resulting in dysfunction of these proteins is associated with diseases of excessive calcification (PXE, generalised arterial calcification of infancy, GACI, or calcification of joints and arteries, CALJA). On the other hand, proteins shown in orange act to promote calcification by hydrolysing ATP to release P_i (NTPD1) or breaking down PPi into Pi (TNAP). Genetic dysfunction of these proteins results in systemic hypophosphatasia and spastic paraplegia type 64 (SPG64). High TNAP activity had an inverse correlation with PP_i levels in PXE patients compared with age matched controls[65].

Serum [PP_i] would then appear to be a useful measure of a tendency to dystrophic calcification, and yet there are technical challenges to this measurement[66,67]. Pyrophosphate may also be released by activated platelets during venepuncture, falsely elevating levels[68]. Technical developments may facilitate clinical testing of serum PP_i levels[69], and yet there is weak correlation between circulating PP_i and arterial calcification complications in PXE[67]. Fundamentally PP_i is difficult to measure consistently, and serum levels fluctuate greatly with food intake and other factors, and it will always be a weak indicator of calcification, in the same way that current rainfall is a weak indicator of lake level[70].

Future directions

Currently, there are no disease modifying treatments for PXE or ODD: patients with the former are advised to avoid eye injuries and given an Amsler grid, and the latter are sometimes treated with glaucoma medication (if intraocular pressure is raised or field loss is progressive). Treatments to reverse or halt the ectopic calcification to prevent progressive optic neuropathy in ODD would be desirable. A range of potential treatment options for PXE have been proposed, including gene therapy to increase ABCC6 or NPP1 function, TNAP inhibition, and a range of weaker calcification inhibitors such as magnesium or vitamin K[48], but the first trials have been PP_i supplementation or the bisphosphonate etidronate[71]. In PXE, vitamin D and calcium supplementation have been associated with worsening vascular calcification in the long term[72].

Etidronate is a molecular analogue of PP_i that is harder to degrade by alkaline phosphatases. Bisphosphonate medications became popular for osteoporosis as they inhibit osteoclasts (reducing bone loss), but they also inhibit HA formation as a potent and long-acting analogue of PP_i which bind and accumulate in bone. Later generations of bisphosphonates increased the former, desired, effect on osteoclasts while reducing the inhibition of mineralisation[73], and thus etidronate is not favoured as a treatment for osteoporosis but it would be the potentially most useful bisphosphonate for treating ectopic calcification.

Etidronate administered to *Abcc6*$^{-/-}$ mice reduced development of ectopic skin calcification but did not reverse pre-existing dystrophic calcification[74]. An important human randomised trial of etidronate for PXE found that it halted arterial calcification[71,75], but did not affect choroidal neovascularisation when adjusted for eye disease at baseline[76]. These promising initial results have not yet been followed up in other patient groups as etidronate was lost from the market in recent years.

During initial work observing the *Abcc6*$^{-/-}$ mouse, it was recognised that PP_i in the animal diet was sufficient to suppress the ectopic calcification phenotype, with obvious therapeutic implications for patients with PXE[77,78]. Many foods and common ingredients such as baking powder contain high levels of PP_i. However, therapeutic supplementation of PP_i has challenges, as it is rapidly split into P_i in the gut, and in circulation, so an oral dose of PP_i becomes a large dose of P_i and a small short-lived increase in serum PP_i[79]. This can cause hyperphosphataemia and requires healthy kidneys to process, and yet PP_i is 'generally recognised as safe' – a non-toxic physiological metabolite with high maximal tolerable daily intakes[77]. Oral formulations of PP_i have been developed to improve bioavailability and safety, for example, a gelatin-encapsulated sodium dihydrogen pyrophosphate ($Na_2H_2P_2O_7$), or a sodium-free ($K_2H_2P_2O_7$)[80], and tetrasodium pyrophosphate ($Na_4P_2O_7$)[81]. A prospective randomised trial of PP_i supplementation for patients with PXE is underway (PROPHECI-PPI, ClinicalTrials.gov NCT04868578). Biomarkers of calcification in the eye, such as the reflectivity of Bruch membrane or the presence and size of ODD, will be helpful in translating these results to people with simple isolated ODD.

Other approaches for treating PXE are also under investigation, such as inhibiting TNAP with the commonly available proton pump inhibitor lansoprazole[82]. To understand which options are potentially of greatest benefit for PXE patients, or patients with inherited anaemias or simple ODD, will require comparing the long term effects on bone mass and other potential side effects relating to high or low P_i levels.

Conclusions

Optic disc drusen are a common type of ectopic calcification in the eye. The strongest systemic association is with PXE, which highlights the ABCC6 protein and the role of PP_i in systemic ectopic calcification. While PPi supplementation is an appealing potential treatment, there are challenges with measuring PPi and supplementing it, and trials for PXE will inform the possibility of treatment for our patients with ODD.

Conflicts of Interest Statement:

The authors declare no conflicts of interests.

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