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REVIEW ARTICLE

NAION or not NAION? A literature review of pathogenesis and differential diagnosis of anterior ischaemic optic neuropathies

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PURPOSE: To offer a comprehensive review of the available data regarding non-arteritic anterior ischaemic optic neuropathy and its phenocopies, focusing on the current evidence to support the different existing aetiopathogenic hypotheses for the development of these conditions.

CONCLUSIONS AND IMPORTANCE: Due to the limited array of responses of the neural tissue and other retinal structures, different aetiopathogenic mechanisms may result in a similar clinical picture. Moreover, when the insult occurs within a confined space, such as the optic nerve or the optic nerve head, in which different tissues (neural, glial, vascular) are highly interconnected and packed together, determining the primary noxa can be challenging and may lead to misdiagnosis. Anterior ischaemic optic neuropathy is a condition most clinicians will face during their everyday work, and it is important to correctly differentiate among resembling pathologies affecting the optic nerve to avoid unnecessary diagnostic procedures. Combining a good clinical history and multimodal imaging can assist diagnosis in most cases. The key remains to combine demographic data (e.g. age), with ophthalmic data (e.g. refractive error), systemic data (e.g. comorbidities and medication), imaging data (e.g. retinal OCT) with topographic signs (e.g. focal neurology).

METHODOLOGY: Papers relevant for this work were obtained from the MEDLINE and Embase databases by using the PubMed search engine. One author (MPMG) performed the search and selected only publications with relevant information about the aetiology, pathogenic mechanisms, risk factors as well as clinical characteristics of phenocopies (such as vitreopapillary traction, intrapapillary haemorrhage with adjacent peripapillary subretinal haemorrhage or diabetic papillopathy) of non-arteritic anterior ischaemic optic neuropathy (NAION). The terms "non-arteritic ischaemic optic neuropathy/NAION", "vitreopapillary traction", "vitreopapillary traction AND non-arteritic ischaemic optic neuropathy/NAION", "posterior vitreous detachment AND non-arteritic ischaemic optic neuropathy/NAION", "central retinal vein occlusion AND non-arteritic ischaemic optic neuropathy/NAION", "disc oedema/disc oedema", "diabetes mellitus AND non-arteritic ischaemic optic neuropathy/NAION" and "diabetic papillopathy" were searched on PubMed. From each of these searches, publications were selected based on their title, obtaining a total of 115 papers. All papers not written in English were then excluded, and those whose abstracts were not deemed relevant for our review, according to the aforementioned criteria. Subsequent scrutiny of the main text of the remaining publications led us (MPMG, AP, ZS) to include references which had not been selected during our first search, as their titles did not contain the previously mentioned MeSH terms, due to their significantly relevant contents for our work. A total of 62 publications were finally consulted for our review. The literature review was last updated on 24-Aug-2022.

Eye; https://doi.org/10.1038/s41433-023-02716-4

INTRODUCTION

Non-arteritic anterior ischaemic optic neuropathy (NAION) is an important cause of acute visual loss in the middle-aged and elderly populations [1]. It is mainly characterised by sudden, painless vision loss, relative afferent pupillary defect (RAPD), decreased colour perception, hyperaemic optic disc swelling and visual field (VF) defects [2–5]. Flame-shaped haemorrhages may also be present at or near the disc [2, 6], whereas cotton wool spots are unusual [7]. About half of patients may present with relatively good best corrected visual acuity (BCVA > 6/9) immediately after NAION [3]. Although it has been suggested that BCVA may improve over time in a proportion of patients, this may actually be the result of patients with a central VF defect having learned to fixate eccentrically [3, 8]. VF defects are universally found in patients with NAION, the most common pattern being a combination of relative inferior altitudinal defect with an absolute inferior nasal defect [2]. The clinical picture of NAION may sometimes resemble other pathologies [9], and currently there is no consensus about treatment for the acute stages, although some medical as well as surgical therapies have been considered [2, 5, 10].

The association of central retinal vein occlusion (CRVO) with NAION [6, 11, 12] has been reported in literature. Interestingly, both conditions are said to share some risk factors, such as systemic arterial hypertension, diabetes mellitus, hyperlipidaemia or hypercoagulable states. CRVO typically presents with

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Received: 7 June 2022 Revised: 26 July 2023 Accepted: 25 August 2023

superficial and deep haemorrhages in all four quadrants of the peripheral retina, along with variable degrees of venous tortuosity and dilation, optic disc swelling, cotton wool spots and frequently cystoid macular oedema. RAPD may also be present in ischaemic CRVO. Fluorescein angiography (FA) typically shows normal choroidal filling and a variable delay of retinal vascular filling due to obstruction to the venous outflow in the early stages, whereas the late phases may reveal peripheral capillary non-perfusion, variable macular leakage and staining of the optic nerve head (ONH) [13].

Some authors have reported the association between posterior vitreous detachment (PVD) and vitreopapillary traction (VPT) syndrome with NAION [14–16]. PVD requires both weakening of vitreoretinal adhesion and vitreous liquefaction, and these must occur to an equal extent for the process to be uneventful. An imbalance of these two in favour of liquefaction might result in traction at the sites of persistent adherence, as the vitreous body contracts due to loss of volume [17]. VPT consists of anteroposterior traction exerted on the optic disc due to vitreous attachment to the surface of the ONH, which may result in morphologic alterations of the optic disc and subsequent optic disc swelling, intra- or peripapillary haemorrhages. It has also been hypothesised to cause visual function decline, as it may induce neuronal dysfunction as well as decreased prelaminar flow, which, in turn, has been suggested to lead to NAION [14–17]. VPT may be seen on optic disc OCT scans as vitreous bands adherent to the ONH, detached from the retinal surface and vertically oriented.

Although arteritic anterior ischaemic optic neuropathy (AAION) is another type of anterior optic neuropathy, its well-established association with giant cell arteritis differentiates it aetiopathogenically with the other anterior ischaemic optic neuropathies discussed in this review. Other non-vasculopathic factors, such as optic disc drusen and peripapillary hyperreflective ovoid mass-like structures (PHOMs), have been suggested to play a role in the development of NAION [18], particularly in young patients. However, they will not be discussed in this review, as their contribution to local ischaemia in the ONH is thought to be secondary to a mass occupying lesion effect.

It is our aim with this work to provide an overview of the current evidence for pathogenesis in NAION and provide a differential diagnosis for this entity.

RESULTS AND DISCUSSION

Traditional model for NAION pathogenesis

The clinical features of NAION are well-known amongst clinicians and have been extensively reported in literature. However, the pathogenic mechanism for NAION appears to be poorly understood.

The traditional model for NAION implies that acute ischaemia at the ONH impairs orthograde axonal transport, resulting in axonal oedema. This in turn would create a compartment syndrome in predisposed patients (those with crowded discs), that ultimately leads to infarction in the retrolaminar portion of the ONH, axonal degeneration and apoptosis of retinal ganglion cells [19, 20].

Vasculopathic factors

Precipitating events, such as nocturnal hypotension, or impaired autoregulation of the microvascular supply of the optic nerve, may result in optic nerve ischaemia [20]. A study by Landau et al. showed mean lower blood pressure in patients with anterior ischaemic optic neuropathy, although it was not stated whether it was arteritic anterior ischaemic optic neuropathy (AAION) or NAION, but no statistical differences with matched controls with regard to overnight nadir pressure. They noticed that the blood pressure rise curve in the early morning was less steep and more irregular in the patient group, and whilst not statistically significant, they suggested this may explain why AION occurs mainly on awakening [21]. The authors suggested that chronic hypoperfusion of the optic nerve due to lower blood pressure may be a sign of autoregulatory dysfunction implicated in the pathogenesis of anterior ischaemic optic neuropathy [21]. Hayreh et al. also found nocturnal hypotension in a cohort of 166 patients with ocular ischaemic disorders, but their results are controversial due to the lack of matched controls [22]. Also hypertension, phosphodiesterase-5 inhibitors, serotonin and endothelin-1 have been suggested to have a role as vascular autoregulation modifiers, and therefore in the pathogenesis of NAION [20, 22].

Most investigators, however, support vasculopathic occlusion of branches of the short posterior ciliary arteries (SPCAs) as the main cause for ischaemia in NAION. The defenders of this hypothesis rely on mainly two notions: (i) that vasculopathic risk factors are found in the majority of NAION patients [1] (although Beri et al. did not find any vascular risk factors in 28% of patients in a series of 388 patients with NAION [23], and Levin et al. proposed that these are not specific for arterial disease [24]), and (ii) that the delayed filling of the prelaminar portion of ONH on FA [25–27] indicates that the origin of the hypoperfusion occurs distal to the split of the choroidal branches of the SPCAs, that is, it is located at the paraoptic branches of the SPCAs or their tributaries [25]. These studies show that the optic disc filling defects appear to be sharply demarcated and aligned along the horizontal midline of the disc, which could be closely related to the anatomy of the annulus of Zinn, which provides blood supply to the ONH from branches of the SPCAs and is divided into a superior and an inferior portion. If either the superior or inferior portion of the annulus of Zinn is affected due to hypoperfusion from the SPCA distal branches, this would result in altitudinal VF defects in patients affected with NAION, and further support a primary vascular disease as the pathogenic mechanism in this condition as stated by Arnold et al. [25]. Figure 1 shows a schematic diagram of vascularisation at the level of lamina cribrosa and optic nerve head, and the suggested site of SCPA occlusion.

However, the same authors acknowledged in their study that optic disc filling delay: (i) may also be secondary to any cause of intra-axonal swelling, not only vascular, and (ii) does not necessarily imply optic nerve damage, given that other non-ischaemic optic nerve conditions, such as papillitis and papilloedema [27] also show optic disc filling delay during FA [25]. In conclusion, although the aforementioned findings may suggest retrolaminar hypoperfusion in patients with NAION secondary to SPCAs damage, this cannot be conclusively demonstrated angiographically, given that only the prelaminar region of the ONH can be examined during this test, while the deeper layers remain poorly visualised [28].

Diabetes mellitus has been suggested as another vasculopathic factor for the development of NAION [29, 30]. Damage of the vascular endothelium, along with pericyte loss, thickened basement membranes and increased leukostasis caused by diabetes mellitus may lead to abnormal vascular haemodynamics, such as dispersion of nutrients and reabsorption of fluid and waste, and capillary vasostasis. These microvascular abnormalities may cause hypoperfusion and ischaemic damage at the level of the ONH For this reason, diabetes mellitus may constitute a risk factor for NAION development.

Diabetes mellitus can lead to another phenotype in the clinical spectrum of NAION, “diabetic papillopathy”. A typical diabetic papillopathy is characterised by unilateral or bilateral, hyperaemic optic disc swelling with superficial teleangiectasias and leakage on FA, and it typically has a milder, more transient course than NAION [31]. NAION and diabetic papillopathy may present with similar clinical features in the initial presentation. However, they differ in subsequent structural damage as evidenced by OCT

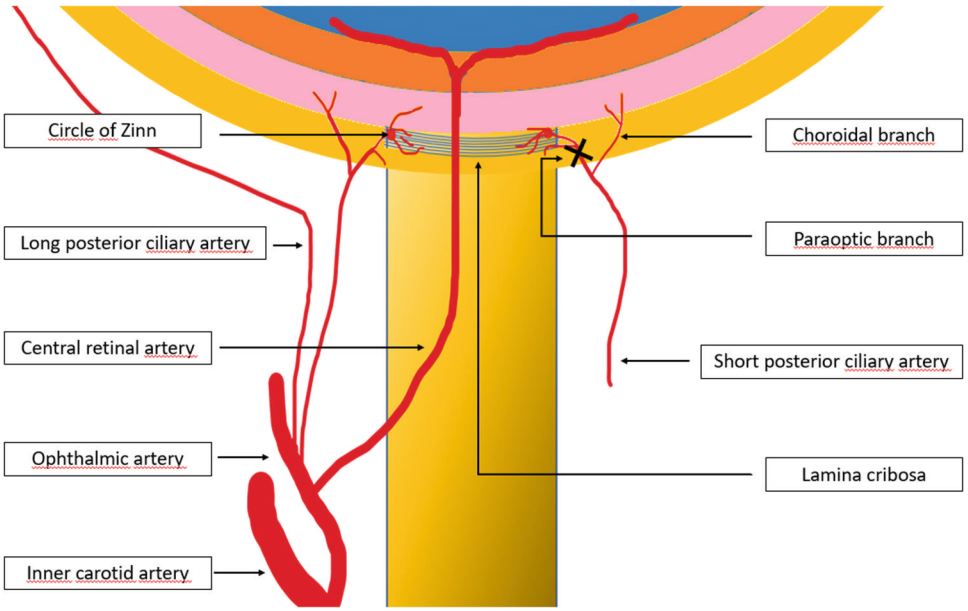

Fig. 1 This diagram depicts the proposed site of occlusion of the short posterior ciliary arteries (SPCAs) as the most widely accepted cause of ischaemia in non-arteritic anterior optic neuropathy (NAION). The location of the suggested occlusion would be distal to the bifurcation of SCPAs into paraoptic and choroidal branches. The reason to propose that occlusion occurs at this level is the delay of prelaminar optic disc filling (whose blood supply mainly depends on the paraoptic branches of the SCPAs) and the lack of choroidal filling delay on fluorescein angiography (FA), which suggests normal perfusion from the choroidal branches of the SCPAs. It is important, however, to remark that histopathological evidence for this hypothesis is lacking.

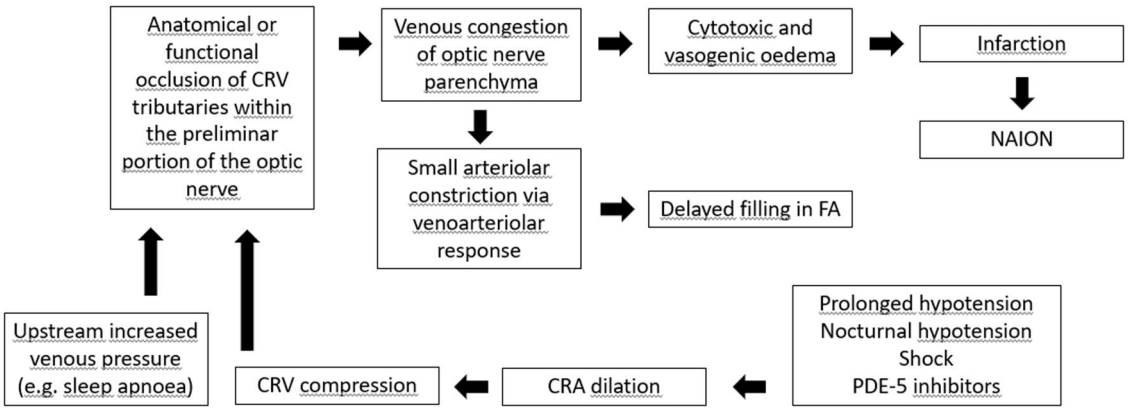

Fig. 2 Flowchart depicting the venous aetiology for ischemia in NAION as proposed by Levin et al. Prolonged hypotension, nocturnal hypotension, shock and/or PED-5 inhibitors would be the primary causes that would lead to a sequential cascade of events resulting in delayed filling in fluorescein angiography and, finally, NAION.

changes, as both may show thinning of the retinal nerve fibre layer and macular ganglion cell layer, but thinning of the macular inner nuclear layer, typically present in NAION, is not observed in diabetic papillopathy [31]. Also, although the exact aetiopathogenic mechanism of a diabetic papillopathy has not been fully elucidated, it seems to be different to the acute onset of ischaemia in NAION. The ischaemic damage in diabetic papillopathy is understood to be secondary to chronic hypoperfusion in the microvasculature of the ONH subsequent to vascular endothelium damage, pericyte loss, thickened basement membranes and increased leukostasis [31–34]. The prognosis is generally good.

It has been previously reported that in diabetic patients, the posterior vitreous cortex is particularly adherent to the optic disc [35], and could exert some traction over the ONH; however, there appears to be little evidence to link this phenomenon to diabetic papillopathy, and therefore it seems unlikely that this form of anterior ischaemic optic neuropathy is in any way related to VPT, which, if present, may well be secondary to the presence of fibrovascular tissue in eyes with proliferative diabetic retinopathy.

Histopathology and doppler flow studies

Histopathologic studies in patients diagnosed with NAION are scarce, and some include atypical cases [36–40], while others demonstrate infarction of the optic nerve, but lack clinical correlation [41, 42]. Quigley et al. reported the case of one patient in a series of 3, who presented with clinical findings of typical NAION, and was demonstrated to have evidence of optic nerve infarction, that did not correspond to the territory of a particular artery [37]. Unfortunately, the study of this eye was performed long after the onset of NAION, when optic atrophy was well established. Therefore, histopathologic data of the optic disc microvascular supply in acute NAION is lacking.

Three studies analysed optic nerve blood flow in NAION using colour doppler flow and laser doppler flow. However, they failed to demonstrate any conclusive localised circulatory impairment in NAION, mainly due to controversial assumptions of the haemodynamics in the studied area and technical limitations [28, 43, 44].

Venous aetiology

Some authors believe that there is insufficient evidence for NAION to be considered a primary arterial disease, especially in the absence of histopathologic confirmation. Levin et al. compared clinical findings in NAION to those observed in AAION, a known disease of arterial origin, in which SPCAs occlusion has been histopathologically documented. AAION presents with a pale, swollen disc, with marked tissue loss and excavation at the disc, occasionally with disc haemorrhages, and severe visual loss, as opposed to the hyperaemic swelling, relatively preserved disc substance, frequent disc haemorrhages and usually milder visual loss seen in NAION. These differences, and their similarity to the findings seen in cerebral infarcts of arterial and venous origin, respectively, led them to conclude that NAION is likely a primary venous occlusive disease [24]. They subsequently hypothesised that NAION may be due to impaired flow of the venules that receive blood from the optic disc capillaries and drain into the central retinal vein (CRV), posterior to the surface of the ONH. Functional occlusion of these venules may result in venous congestion of the optic nerve parenchyma and subsequent cytotoxic and vasogenic oedema at that level. Initial disc oedema would in turn lead to a compartment syndrome that would eventually cause infarction and tissue loss at the level of the ONH. Conditions that may cause increased venous pressure, such as sleep apnoea or upstream venous congestion, may therefore have a role in the pathogenesis of NAION. Also, given that the CRV and the central retinal artery (CRA) share their sheath, dilation of the CRA (which occurs with prolonged hypotension, nocturnal hypotension, shock or phosphodiesterase-5 inhibitors, all of them reported in association with NAION [7, 20]) could compress the CRV, causing localised venous congestion and initiating a compartment syndrome. Levin et. al propose venous congestion at the level of the prelaminar portion of the ONH causes localised constriction of small arteries via the arteriovenular response, explaining the slower disc filling that may be seen in FA in NAION [24]. Figure 2 shows a flow chart summarising the mechanisms explained in this section.

Vitreopapillary traction hypothesis

Other authors proposed that vitreous forces may play a role in the pathogenesis of NAION [14–17]. Numerous reports in literature describe VPT to cause disc elevation and alterations in the ONH structure [14, 16, 17, 45–52], haemorrhages and irregular dilatation of the surface vessels [16, 47, 48, 53, 54], RAPD [14, 45, 47, 48, 51], and also decreased visual function, including BCVA, VF and visual-evoked potentials (VEP) [16, 45–49, 52, 55]. Vitreous forces exerted by proliferation of fibrous astrocytes, myofibroblasts, fibrocytes, and retinal pigment epithelial cells, may cause traction on the ONH. This latter may be variable and cause asymptomatic elevation in some cases, or symptomatic swelling of the ONH in others, which has been hypothesised to eventually lead to NAION [14–17]. This hypothesis suggests that traction on the ONH may lead to elongation of the optic nerve fibres as well as its nourishing blood vessels. This would subsequently cause disc swelling due to axonal cytoskeletal damage and axoplasmic flow impairment, and to a mechanical reduction of the calibre of the microcirculation in the ONH, resulting in reduced perfusion and ischaemia. Ischaemia, therefore, would still play an important role in pathogenesis in this hypothesis, although not as the primary cause of NAION. Figure 3 depicts the case of an 86-year-old woman with tomographic evidence of VPT in her right eye.

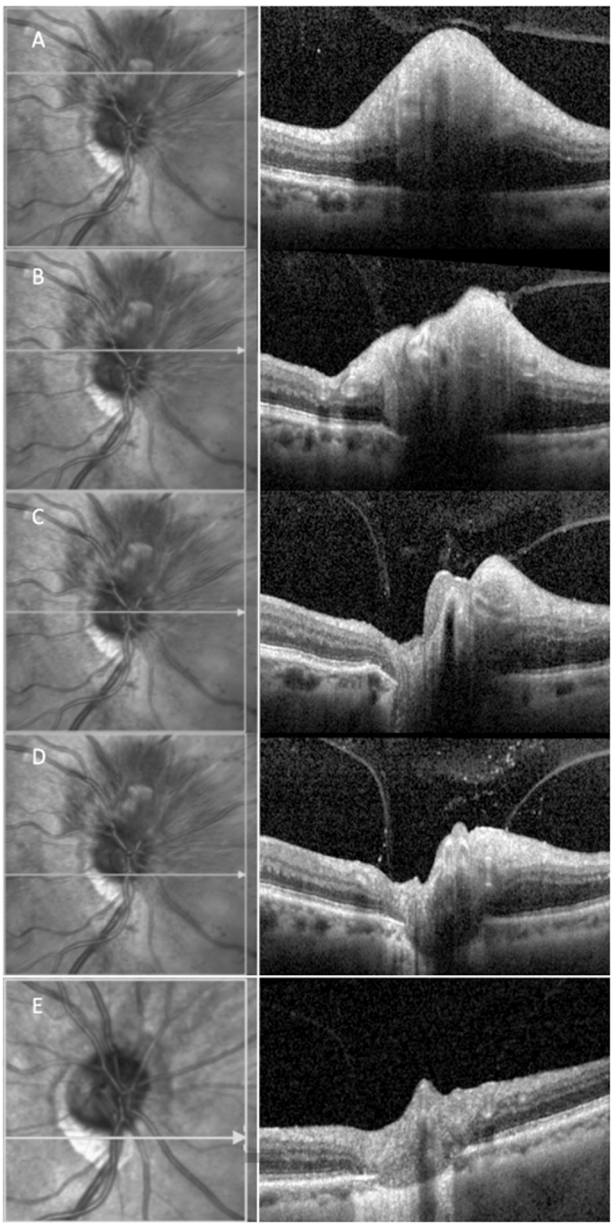

Fig. 3 OCT Spectralis scans through the right optic disc of an 86-year-old female. The patient presented with haemorrhages obscuring the superior quadrant of her right optic disc, associated with central retinal vein occlusion (CRVO). The images exhibit sequential cuts through the optic disc, superiorly to inferiorly from top to bottom. **A**–**D** There is significant swelling of the optic disc, more markedly superonasally. Note the hypereflective vitreous bands, vertically oriented, and the beginning of a vitreous detachment in the more superior cut. The hyperreflective dots overlying the optic disc head represent vitreous haemorrhage. **E** Repeat optic disc scans over the subsequent 5 months demonstrated sectoral optic disc atrophy consistent with a diagnosis of NAION, whilst the vitreopapillary adhesions remained unchanged (note the fine hipereflective vitreous bands, vertically oriented, in a similar disposition as in previous OCT scans).

Some studies proposed that the changes seen on ONH due to VPT may be reversible, and prompt traction release via pars plana vitrectomy may lead to functional and anatomical improvement [14, 15, 55, 56], and may preclude permanent optic nerve damage [56]. Modarres et al. performed pars plana vitrectomy on 16 patients with partial PVD within one month of onset of NAION.

Only one OCT scan clearly revealed tomographic signs of VPT, while the other 3 OCT scans showed in the paper exhibited vitreopapillary attachment. They found that most of the patients improved their visual function after vitrectomy and concluded that vitreous traction may have a causative role in some cases of NAION [15]. Kroll et al. reported an increase in BCVA and improvement in VEP responses in some of their patients with VPT after vitrectomy; however, only cases of proliferative diabetic retinopathy were included in this cohort [56]. It is also important to notice that these studies included a limited number of patients and were not controlled. Also, it is not infrequent that patients with NAION show some degree of improvement in their visual function overtime [3]. Shen et al. reported the case of a patient diagnosed with NAION whose symptoms worsened at the time of a PVD in the same eye, and later improved. They concluded that the traction caused by the vitreous on the ONH prior to separation caused the worsening in symptoms, which would be in line with the aforementioned theory. However, imaging of the ONH prior to PVD is lacking, so VPT could not be demonstrated [14]. Parsa et al. claimed that the evidence for ischaemia as the primary cause for NAION remains insufficient, and supported that vitreopapillary attachments, which are especially firmer on cup less discs, may eventually lead to the onset of NAION. They proposed to rename NAION as "papillary vitreous detachment neuropathy", PVD-N [16]. Whilst this manuscript was under review a modified interpretation of the hypothesis was published [57].

Other authors disagreed with this hypothesis, especially in regards to the evidence of ischaemia in NAION [58, 59]. However, the VPT hypothesis states that ischaemia may not be the primary event in NAION, but does not set it aside [15, 16, 56]. Other authors focus on the proportion of vitreous attachment and PVD in NAION. Lee et al. suggested that the low proportion of vitreous attachment in their cohort of 26 eyes with NAION, 35%, argues against traction as a major contributor to the pathophysiology of NAION [60]. Conversely, Thompson et al. and Hayreh et al. found 30% and 25.3% of vitreous detachment in their cohorts of 74 and 198 patients with NAION, respectively, and a similar proportion in the fellow eyes [19, 61]. Also, 8 of the patients in Thompson et al.'s cohort had a confirmed PVD prior to NAION. They argued that if the pathogenesis of NAION was primarily mechanical, PVD should be actively developing at the time of the acute NAION, and complete PVD should preclude the development of NAION. Based on the data from their cohort, they do not support that vitreous forces have a direct role in the pathogenesis of NAION [19].

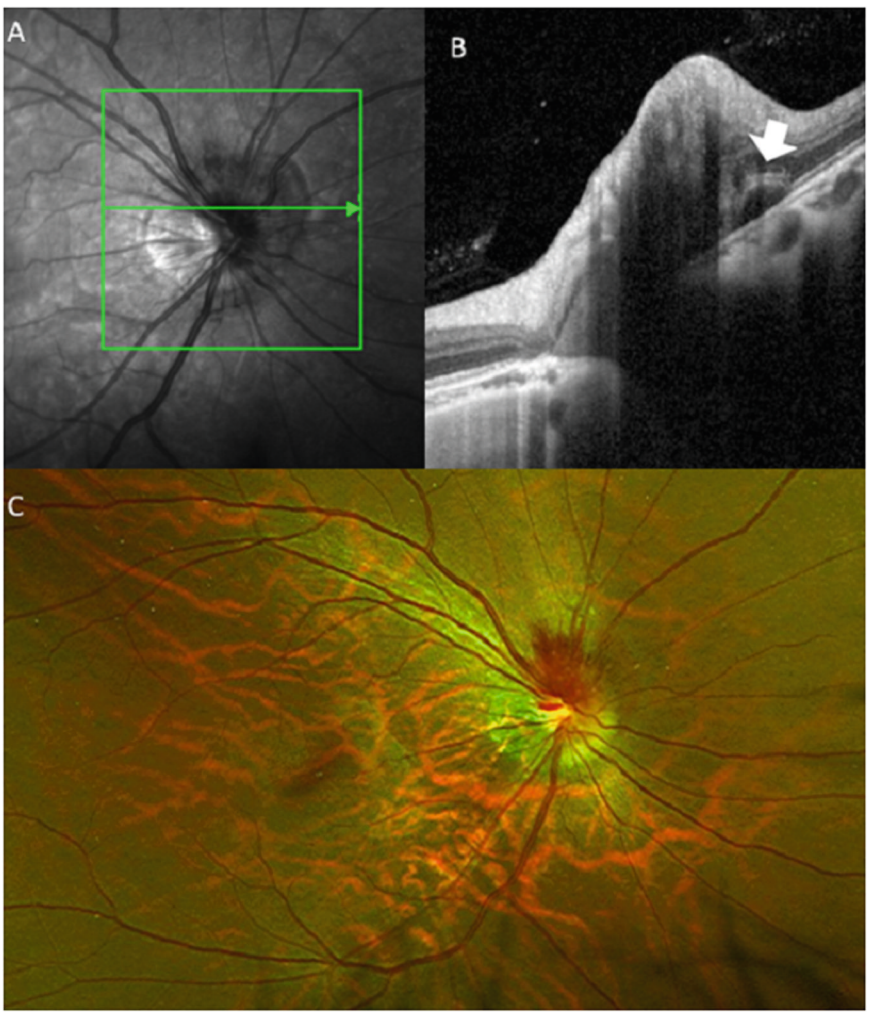

Fig. 4 Multimodal imaging of a 22-year-old female, who was diagnosed with intrapapillary haemorrhage with adjacent peripapillary subretinal haemorrhage (IHAPSH) in her right eye. The patient was myopic and of Asian descent; she had few symptoms and denied any recent Valsalva manoeuvres. Complete resolution of the haemorrhage was observed 10 weeks after presentation. **A**, **B** Spectralis OCT through her right optic disc. Note the tilted disc and the subretinal haemorrhage (white arrow) adjacent to the optic disc on its supero-nasal quadrant. **C** Fundus pseudocolour image of the patient´s right eye. The intrapapillary haemorrhage in the supero-nasal quadrant of the optic disc is evident.

Fig. 5 Fundus pseudocolour image of the right eye of an 86-year-old female diagnosed with non-arteritic anterior optic neuropathy (NAION). This is the same patient as in Fig. 3. Note the intra- and peripapillary haemorrhages obscuring most of the optic disc. Cotton wool spots can be seen on the superior quadrant of the optic disc. Intraretinal haemorrhages in all 4 quadrants and vitreous haemorrhage could be consistent with a diagnosis of central retinal vein occlusion (CRVO), although venous tortuosity and dilation were not evident. We hypothesise that swelling of the optic disc secondary to NAION may have led to secondary venous congestion in the central retinal vein.

However, they acknowledged the existence of a distinct clinical entity, VPT- optic neuropathy (VPTON), which presents with disc haemorrhages, elevation of the ONH and leakage of the ONH on FA secondary, which may resemble clinical features of NAION if presented unilaterally [19].

This latter condition may be similar to what Kokame et al. have termed intrapapillary haemorrhage with adjacent peripapillary subretinal haemorrhage (IHAPSH) [53], which has been described in relation to optic disc traction due to vitreous attachment in some cases. This condition seems to occur more frequently in myopic young patients of Asian origin, with tilted discs and optic disc swelling in some cases [53]; however, it has also been reported in non-myopic and Caucasian patients with crowded discs [53, 54], in all age groups (11–79 years) [53, 54, 62]. These patients present with peripapillary haemorrhages alone or concomitant with intrapapillary haemorrhages, usually superonasally and unilaterally, associated with mild or no visual symptoms [53, 54, 62], and with preservation of optic nerve function [62]. Kokame et al. also described vitreous haemorrhage in association with IHAPSH [53], and Katz et al. hypothesised thar vitreous attachment to the ONH may traumatise and tear optic disc superficial vessels, causing haemorrhages in and around the disc; also, transmission of the force through the retina may well cause subretinal bleeding [62]. Nevertheless, clear tomographic evidence of VPT in these cases is lacking, and some authors have proposed a mechanical hypothesis for this condition precipitated by acute disc oedema, Valsava manoeuvre, apart from VPT, given the elevated nasal edge of the myopic tilted discs and the subsequent traction this exerts on the choroidal blood supply of the prelaminar optic nerve [53]. Clinical features of IHAPSH are shown in Fig. 4.

Association with CRVO

Abu El-Asrar et al., Kim et al. and Raman et al. have reported CRVO in association with NAION [6, 11, 12]. The patients reported in these papers were all below 50 and 3 of them had confirmed thrombophilic factors. Similarly to other conditions in which optic disc swelling has resulted in compression of the CRV and led to CRVO, such as pseudotumor cerebrii, optic disc drusen, optic neuritis and optic nerve glioma [6], it has been suggested that mechanical obstruction of the CRV by the swollen optic nerve could have predisposed to CRVO [6, 11]. In addition, clinical

Table 1. The table offers a quick and easy overview of the various entities: (i) NAION, (ii) VPT/VPTON, (iii) diabetic papillopathy, (iv) IHAPSH and (v) CRVO, focusing on clinical criteria, patients' demographic features and tomographic findings, and also includes the proposed aetiopathogenesis for each entity.

	NAION	VPT/VPTON	Diabetic papillopathy	IHAPSH	CRVO
Demographic features	Typically >50 years	Typically aging population (but reported cases from 3rd decade on)	Younger patients (DM type 1), older (DM type 2)	All age groups, typically young and Asian patients	Typically >50 years
Refractive error	–	Typically myopic	–	Typically myopic	–
Symptoms	Persistent visual acuity loss, VF defects, RAPD	Visual acuity loss, gaze-evoked amaurosis, phosphenes, VF defects	Asymptomatic or transient symptoms (blurred or distorted vision)	Transient symptoms (visual acuity loss, floaters)	Variable visual acuity loss
Onset	Acute onset	Insidious onset	Insidious onset	Acute onset	Acute onset
Clinical findings	Hyperaemic disc swelling ± flame peripapillary haemorrhages	Disc elevation, alterations in the ONH structure, peripapillary haemorrhages, irregular vessel dilatation	Hyperaemic disc swelling with teleangiectasias	Peripapillary ± intrapapillary ± vitreous haemorrhages	Hyperaemic disc swelling, venous tortuosity and dilation ± peripapillary flame and/or numular peripheral haemorrhages ± cotton wool spots ± cystoid macular oedema
OCT findings	Optic disc swelling on acute stage, frequently segmental optic nerve head atrophy after resolution (total or partial)	Vitreopapillary traction	Optic disc swelling of the ONH followed by variable retinal nerve fibre layer thinning	Vitreopapillary traction in some cases; tilted disc in some patients	Optic disc swelling on acute stage
Aetio-pathogenesis	Capillary hypoperfusion	Elongation of the optic nerve fibres and vessels due to traction, with subsequent hypoxia	Capillary vasostasis	Mechanical vascular damage in tilted discs vs VPT	Cardiovascular risk factors, especially arterial hypertension

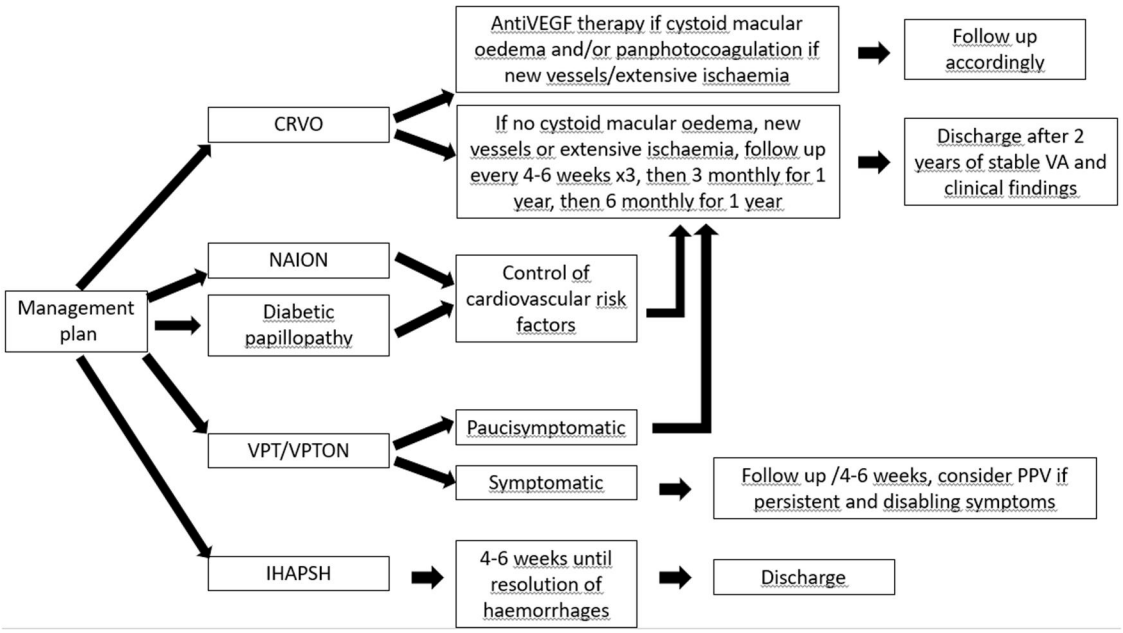

Fig. 6 Flowchart exemplifying management of patients diagnosed with anterior vasculopathic optic neuropathy in our clinic. Note that for some entities, especially those in which a surgical treatment is not needed, management may be similar.

presentation of CRVO, typically showing acute visual acuity loss and RAPD in severe cases, the presence of vasculopathic factors in most patients with CRVO, and hyperaemic, swollen optic disc, with peripapillary haemorrhages in some cases, may resemble NAION, thus constituting a possible NAION simulator. Figures 3 and 5 show disc OCT and retinal photos of an 86-year-old woman diagnosed with NAION and CRVO in her right eye.

CONCLUSION AND RECOMMENDATIONS

Recent developments with OCT imaging of the optic nerve can help differentiate conditions with similar clinical features, such as NAION, VPT/VPTON, diabetic papillopathy, CRVO and IHAPSH, which in occasions may be challenging to diagnose based on fundoscopic findings alone, and serial optic nerve imaging can help identify evidence of progressive changes.

To aid differentiating between the various conditions that have been have discussed in this work, a summary of key features is presented in Table 1 and their proposed management summarised in Fig. 6.

It is our purpose with this work to facilitate the diagnosis as well as management of a number of conditions with different aetiopathogenic mechanisms that may resemble NAION in clinical presentation. However, despite the ever-growing information and evidence, the exact pathophysiology of some of these conditions remains elusive, and further research in this field will need to include OCTA.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

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AUTHOR CONTRIBUTIONS

All authors attest that they meet the current ICMJE criteria for Authorship. MPMG was responsible for conducting the literature search, extracting and analysing data, updating reference lists and writing the report. AP and ZS analysed data and interpreted results, as well as revised and contributed to writing the report.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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