

REVIEW

Ocular and Genetic Risk Factors in Branch Retinal Vein Occlusion: a Comprehensive Review

Christina GARNAVOU-XIROU^{a, b}, Georgios BONTZOS^a, Georgios SMOUSTOPOULOS^a, Stavros VELISSARIS^a, Alexandros PAPADOPOULOS^a, Efstathios GEORGOPOULOS^a, Panagiotis STAVRAKAS^b, Tina XIROU^a, Vasileios KOZOBOLIS^b

^aDepartment of Ophthalmology, Korgialenio-Benakio General Hospital, Athens, Greece

^bDepartment of Ophthalmology, University Hospital of Patras, Patras, Greece



ABSTRACT

Introduction: Branch retinal vein occlusion (BRVO) is a leading cause of vision impairment globally and the second most common retinal vascular disease leading to blindness. Affecting over 20 million people worldwide, the prevalence of BRVO is expected to increase with the aging population. Branch retinal vein occlusion occurs due to the obstruction of small veins draining blood from the retina, leading to hemorrhages, fluid leakage and retinal damage. Its pathogenesis involves a complex interplay of ocular conditions and genetic predispositions.

Methods: A comprehensive literature search was conducted using PubMed and Google Scholar for articles published between January 2010 and January 2024. The search terms included "retinal vein occlusion", "BRVO" and "risk factors." After initial screening of 642 articles, non-English articles, animal studies and in vitro models were excluded. In total, 63 articles were analyzed for ocular and genetic risk factors associated with BRVO.

Results: Ocular risk factors for BRVO include glaucoma, short axial length and optic disc drusen. Elevated intraocular pressure in glaucoma can compress retinal veins, while short axial length increases the likelihood of venous compression. Optic disc drusen cause vascular anomalies that heighten BRVO risk. Genetic polymorphisms affecting coagulation, endothelial function, inflammation and oxidative stress, such as MTHFR C677T and Factor V Leiden, also influence BRVO susceptibility. Familial clustering and genetic variations in inflammatory pathways further contribute to the risk.

Conclusion: The significant impact of BRVO on vision health underscores the need for comprehensive strategies for early detection, prevention and treatment. Understanding the ocular and genetic risk factors is crucial for developing personalized treatment and effective public health initiatives. Ongoing research into genetic and molecular mechanisms will enhance management approaches and improve patient outcomes.

Keywords: BRVO, vein occlusion, risk factors, diabetes, hypertension.

Address for correspondence:

Georgios Bontzos, MD, PhD

Postal address: Korgialenio – Benakio General Hospital, Athanasaki 11, 11526, Athens, Greece

Tel: +2132068754; email: gbontzos@hotmail.gr

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ABBREVIATIONS

BRVO: branch retinal vein occlusion
 CRVO: central retinal vein occlusion
 IOP: intraocular pressure
 FA: fluorescein angiography
 OCT: optical coherence tomography
 MTHFR: methylenetetrahydrofolate reductase
 PAI-1: plasminogen activator inhibitor-1
 VKORC1: vitamin K epoxide reductase complex subunit 1
 eNOS: endothelial nitric oxide synthase
 SNP: single nucleotide polymorphism
 AGTR1: angiotensin II type 1 receptor
 ACE: angiotensin I-converting enzyme
 MMP2: matrix metalloproteinase 2
 TIMP2: tissue inhibitors of matrix metalloproteinase 2
 SDF-1: stromal-cell-derived factor 1
 CXCR4 - C-X-C chemokine receptor type 4
 APOE: apolipoprotein E
 HDL: high-density lipoprotein
 LDL: low-density lipoprotein
 ox-LDL: oxidized low-density lipoprotein
 PON1: paraoxonase 1

INTRODUCTION

Branch retinal vein occlusion (BRVO) is a major contributor to vision impairment globally, standing as the second most prevalent cause of blindness due to retinal vascular diseases (1). Over 20 million people worldwide are affected by BRVO, a number projected to rise as the population ages (1, 2). Branch retinal vein occlusion occurs when there is an obstruction in one of the small veins that carry blood away from the retina. This blockage leads to a buildup of pressure, resulting in hemorrhages, fluid leakage, and ultimately, damage to the retinal tissues. The exact pathogenesis of BRVO is multifactorial, involving hemodynamic changes, local inflammatory processes and structural alterations in the retinal vasculature (3).

The development of BRVO is often a result of the interplay between ocular conditions and genetic predispositions. For instance, individuals with a genetic predisposition to hypercoagulability may have an amplified risk of BRVO when coupled with ocular conditions such as hypertension or glaucoma. Understanding this inter-

play is crucial for identifying high-risk individuals and tailoring preventive measures accordingly.

Effectively managing and comprehending RVO requires an approach that takes into account the various conditions that predispose individuals to this vascular occlusion. With the consistently higher prevalence of BRVO, the demand for efficient screening, prevention and treatment strategies becomes ever more important. These strategies are crucial not only to reduce the immediate impact of RVO on vision but also to address its broader social and economic consequences. This study seeks to provide an updated overview of the ocular and genetic risk factors linked to BRVO, aiming to explore potential management options for prevention or risk reduction.

METHODS

We searched through PubMed and Google Scholar databases for articles published between January 2010 and January 2024, using the following query terms: (retinal vein occlusion) OR (BRVO) AND (risk factors). We found 642 articles. After the initial abstract screening, all articles not written in English, as well as animal and *in vitro* studies were excluded. For this review, we also included systematic reviews and meta-analyses. In total, 63 articles focusing on the ocular and genetic risk factors for BRVO were further considered for analysis.

OCULAR RISK FACTORS

Glaucoma The association between glaucoma and BRVO is a topic of significant clinical interest, highlighting the delicate interplay between intraocular pressure (IOP) and vascular dysregulation. Glaucoma is characterized by progressive optic neuropathy and visual field loss; it frequently involves elevated IOP, which can significantly influence retinal vascular health (4, 5). Understanding the mechanisms linking these conditions is crucial for developing effective management strategies.

Elevated IOP in glaucoma patients can lead to mechanical compression of the retinal vein, particularly at arteriovenous crossing points within the optic nerve head. This mechanical compression hinders venous blood flow, pro-

moting venous stasis and contributing to the development of BRVO. The increased resistance to venous outflow facilitates the formation of thrombi within the compressed vein segment, acting as a primary mechanism through which glaucoma predisposes individuals to BRVO (6).

Glaucoma is associated with vascular dysregulation at both ocular and systemic levels. Abnormalities in the autoregulation of blood flow in response to IOP changes can lead to ischemic conditions within the optic nerve head (7). These ischemic conditions may extend to the retinal vasculature, thus exacerbating the risk of venous occlusion (8). Furthermore, glaucomatous damage may alter the structural integrity of the retinal vessels, making them more susceptible to occlusive events.

The pathophysiology of BRVO in the context of glaucoma can be summarized in the following mechanisms:

1) mechanical compression – elevated IOP causes mechanical compression of the retinal veins at arteriovenous crossings, particularly within the optic nerve head; this compression disrupts normal venous outflow, leading to venous stasis and thrombus formation (9);

2) ischemia and hypoxia – the impaired autoregulation of ocular blood flow in glaucoma results in ischemic conditions within the optic nerve head; these ischemic conditions can extend to the retinal vasculature, promoting hypoxia and further increasing the risk of thrombus formation (8); 3) vascular endothelial damage – chronic elevated IOP can lead to vascular endothelial damage, which impairs the structural integrity of the retinal vessels; this damage makes the vessels more prone to occlusion and contributes to the development of BRVO (10);

4) inflammation and oxidative stress – glaucoma is associated with increased levels of inflammation and oxidative stress, which can exacerbate vascular endothelial damage and promote thrombogenesis (11).

The association between glaucoma and BRVO highlights the importance of understanding the connection between IOP and vascular dysregulation. Elevated IOP leads to mechanical compression of the retinal veins, promoting venous stasis and thrombus formation, while vascular dysregulation exacerbates ischemic conditions and endothelial damage (12). Glaucoma is associated with vascular dysregulation, both at the

level of ocular blood flow and systemic circulation. Abnormalities in autoregulation of blood flow in response to intraocular pressure changes can lead to ischemic conditions within the optic nerve head (13). These ischemic conditions may extend to the retinal vasculature, exacerbating the risk of venous occlusion (14). Additionally, glaucomatous damage itself may alter the structural integrity of the retinal vessels, making them more susceptible to occlusive events (8, 13).

Effective management of glaucoma, including maintaining optimal IOP and addressing systemic vascular risk factors, is crucial in preventing BRVO and preserving retinal health (15, 16). Further research is needed to elucidate the underlying mechanisms and develop targeted therapies for patients with both glaucoma and BRVO.

Short axial length

Short axial length results in a smaller ocular globe, which can lead to anatomical crowding within the optic nerve head and retinal nerve fiber layer. This crowding increases the likelihood of arteriovenous crossings within the retina, where arterial and venous paths intersect (17). At these crossings, arterial pulsation or structural changes due to systemic hypertension or arteriosclerosis can exert additional mechanical pressure on the retinal vein, increasing the risk of venous compression and subsequent occlusion – a key event in the pathogenesis of BRVO (18).

Short axial length may also affect retinal blood flow dynamics, contributing to alterations in shear stress within the retinal vasculature. The architectural constraints of a smaller globe can affect the laminar flow of blood through the retinal vessels, potentially leading to turbulent flow at arteriovenous crossing points. Turbulent flow can increase endothelial activation and predispose to thrombogenesis by promoting endothelial dysfunction and the accumulation of pro-thrombotic factors at sites of vascular compression (19). Turbulent flow can increase endothelial activation and predispose to thrombogenesis by promoting endothelial dysfunction and the accumulation of pro-thrombotic factors at sites of vascular compression (14).

Epidemiological studies have supported the association between short axial length and increased risk of BRVO. Investigations comparing ocular biometric parameters in patients with BRVO to control groups have consistently identi-

fied shorter axial lengths as a significant risk factor for BRVO (17, 20). These findings underscore the importance of considering ocular anatomical factors in the risk assessment for retinal vein occlusions.

The recognition of short axial length as a risk factor for BRVO has important clinical implications. Ophthalmologists should include axial length measurements as part of the comprehensive evaluation of patients at risk for BRVO. Patients with shorter axial lengths may require closer monitoring for early signs of venous occlusion. Moreover, for patients with short axial length and additional risk factors (e.g., hypertension, diabetes), preventive strategies such as blood pressure control and lifestyle modifications should be emphasized to reduce the overall risk of BRVO.

Optic disc drusen

Optic disc drusen (ODD) are acellular, calcified deposits of hyaline-like material located within the optic nerve head, specifically anterior to the lamina cribrosa. These deposits are present in approximately 0.3-2.4% of the population and are often associated with disrupted axoplasmic flow due to the presence of a small scleral canal and a dysplastic optic disc (21). With aging, these drusen calcify, becoming more visible and altering the appearance of the optic disc. While ODD are generally benign, their presence has been linked to several vascular complications, including retinal vascular occlusions (22).

Optic disc drusen are believed to result from disrupted axoplasmic flow, which may be due to the mechanical stress that neural axons experience as they pass through the narrow scleral canal characteristic of ODD-affected eyes. This mechanical stress can lead to axoplasmic disturbances and ganglion cell death. In younger individuals, ODD are often buried within the optic nerve papillae, which can mimic papilledema. As individuals age, the drusen enlarge and become calcified, leading to a more serrated appearance of the optic disc and increased visibility due to progressive atrophy of the overlying nerve fiber layer (21, 23).

Eyes with ODD exhibit several vascular anomalies, such as venous dilation and tortuosity, vascular loops, abnormal proximal branching with trifurcation, and optociliary shunt vessels. These anomalies can predispose individuals to various vascular complications. Notably, ODD

have been linked to conditions like ischemic anterior optic neuropathy and both retinal artery and vein occlusions (24, 25). The pathogenesis of RVO in the context of ODD involves multiple factors. The narrow scleral canals in ODD-affected eyes create a constricted space that can lead to mechanical compression and vascular disturbances. This compression may cause venous stasis and turbulence, leading to endothelial erosion and thrombus formation (25).

The elevated central retinal venous pressure caused by the enlarged drusen can exacerbate these effects, increasing the risk of CRVO. In some cases, the anatomical disturbances caused by ODD may result in venous congestion and flow turbulence, further contributing to the risk of venous occlusion and subsequent complications such as macular edema and reduced visual acuity (26, 27).

Several studies and case reports have documented the association between ODD and retinal vascular occlusions. For instance, a study by Rothenbuehler *et al* highlighted that BRVO is precipitated by the compression of a major retinal artery by underlying optic disc drusen (25). Additionally, Padhy and Behera reported a case of CRVO in a young patient with ODD, emphasizing the role of drusen in the development of this vascular event (27).

The management of patients with ODD and associated retinal vascular occlusions involves regular monitoring of ocular pressure and visual field assessments, especially in patients with concurrent ocular hypertension. In cases where retinal vein occlusion occurs, treatment options include intravitreal injections of anti-VEGF agents or corticosteroids to reduce macular edema and improve visual outcomes (28, 29).

Preventive measures, such as controlling systemic risk factors like hypertension and hyperlipidemia, are also important in minimizing the risk of vascular occlusions in patients with ODD. Additionally, educating patients about the potential complications associated with ODD and the importance of regular eye examinations can help in early detection and management of these conditions.

Uveitis

Uveitis is an inflammatory condition affecting the uvea, which includes the iris, ciliary body and choroid. This condition can lead to significant

ocular complications, including retinal vascular occlusion. Branch retinal vein occlusion in the context of uveitis is particularly noteworthy but remains a poorly studied phenomenon. It is often categorized under vaso-occlusive retinopathy and is associated with various systemic inflammatory diseases (30–32). The pathophysiological mechanisms behind uveitic BRVO are complex and multifaceted. One widely accepted explanation involves Virchow's triad, which consists of endothelial injury, venous stasis, and hypercoagulability. These factors arise from the systemic inflammatory processes characteristic of uveitis and associated autoimmune conditions. Cytokine cascades during inflammation upregulate procoagulants and suppress the protein C and fibrinolytic pathways, leading to a hypercoagulable state (33, 34).

Ucar *et al* (35) highlight that Behçet's disease (BD) is a significant cause of uveitic BRVO. Other conditions, such as sarcoidosis, tuberculosis, systemic lupus erythematosus (SLE), syphilis and Lyme disease, also contribute to the incidence of BRVO in uveitic patients. The inflammation in these diseases causes endothelial damage and venous stasis, promoting thrombus formation and subsequent venous occlusion (36).

Talat *et al* (37) propose that vasculitis in uveitis results from the perivascular infiltration of lymphocytes onto damaged vessels, leading to thrombotic events. The local inflammatory environment damages the endothelium, facilitating thrombosis. This local vascular inflammation can be compounded by systemic factors such as hypertension, dyslipidemia and steroid use, all of which are prevalent in patients with uveitis and further increase the risk of vascular occlusion. Uveitic BRVO tends to affect younger patients compared to idiopathic BRVO, potentially due to the different underlying pathological processes. These patients often present with symptoms such as blurred vision, floaters and visual field defects. The diagnosis of uveitic BRVO requires a thorough clinical examination, including fundus photography, fluorescein angiography (FA) and optical coherence tomography (OCT). These imaging modalities help identify the extent of vascular occlusion and associated retinal changes.

Behçet's disease, as already mentioned, is a prominent cause of uveitic BRVO, typically presents with panuveitis and retinal periphlebitis, which lead to BRVO. FA is particularly useful in

identifying areas of retinal ischemia and neovascularization, which are critical for planning appropriate management strategies.

The management of uveitic BRVO involves addressing both the underlying uveitis and the vascular occlusion. Anti-inflammatory therapies, including corticosteroids and immunosuppressive agents, are used to control the systemic inflammation. In cases of infectious uveitis, such as those caused by syphilis or Lyme disease, appropriate antimicrobial therapy is crucial (38). For instance, penicillin G remains the treatment of choice for ocular syphilis, while broad-spectrum antibiotics like doxycycline and amoxicillin are used for Lyme disease (39). The visual prognosis for patients with uveitic BRVO varies depending on the severity of the occlusion and the effectiveness of the treatment. Early diagnosis and prompt management of both the underlying uveitis and the BRVO are essential for optimizing visual outcomes. Regular follow-up and monitoring are necessary to detect and treat recurrent or persistent inflammation and to manage complications such as macular edema.

Branch retinal vein occlusion is a significant cause of vision impairment and blindness worldwide. It occurs due to the obstruction of small veins that drain blood from the retina. The pathogenesis of BRVO is complex, involving both environmental and genetic factors. Genetic predispositions play a crucial role in influencing an individual's susceptibility to BRVO. This section explores various genetic polymorphisms associated with BRVO, including those in the coagulation pathway, endothelial function, inflammation and oxidative stress.

GENETIC RISK FACTORS

Genetic polymorphisms in the coagulation pathway

Several polymorphisms in genes encoding proteins involved in the coagulation pathway have been studied in relation to BRVO. These include MTHFR C677T and A1298C, factor V Leiden G1691A, plasminogen activator inhibitor 1 (PAI-1) 4G/5G, factor II (prothrombin) G20210A, and vitamin K epoxide reductase complex subunit 1 (VKORC1) G1639A. However, research has yielded conflicting findings on the association between these thrombophilic mutations and BRVO (40, 41).

MTHFR C677T polymorphism

The MTHFR C677T polymorphism is among the most extensively researched genetic variants in relation to its potential role as a risk factor for BRVO. The MTHFR gene codes for the enzyme methylenetetrahydrofolate reductase, which plays a crucial role in homocysteine metabolism. The C677T polymorphism results in reduced enzyme activity, leading to elevated plasma homocysteine levels, a condition known as hyperhomocysteinemia (42). Several case-control studies have reported an association between the MTHFR C677T genotype and BRVO, while other studies and meta-analyses have not confirmed this association (43).

Factor V Leiden G1691A mutation

Factor V Leiden mutation is another well-studied genetic variant associated with BRVO. This mutation involves a single nucleotide polymorphism (SNP) in the F5 gene, resulting in an arginine-to-glutamine substitution at position 506 (R506Q). Factor V Leiden mutation renders factor V resistant to inactivation by activated protein C (APC), leading to a hypercoagulable state (44). This increased propensity for clot formation can contribute to the development of BRVO. However, a meta-analysis by Romiti *et al* found no significant difference in the prevalence of factor V Leiden mutation between healthy subjects and patients with retinal vascular occlusion (45).

Prothrombin G20210A mutation

Prothrombin G20210A mutation is another genetic variant implicated in BRVO. This mutation is a guanine (G) to adenine (A) substitution at position 20210 in the 3'-untranslated region of the F2 gene, leading to elevated plasma prothrombin levels. Increased prothrombin levels enhance thrombin generation, creating a hypercoagulable state and increasing the risk of thrombosis, including BRVO. Several studies have investigated the association between the G20210A mutation and BRVO risk, with varying results.

PAI-1 4G/5G polymorphism

Plasminogen activator inhibitor-1 (PAI-1) is a key regulator of fibrinolysis. The 4G/5G polymorphism in the PAI-1 gene promoter region influences PAI-1 expression levels, with the 4G allele associated with higher PAI-1 activity (46). Eleva-

ted PAI-1 levels can inhibit fibrinolysis, promoting thrombosis. Some studies have suggested an association between the PAI-1 4G/4G genotype and an increased risk of BRVO, while others have not found significant correlations (47).

VKORC1 G1639A polymorphism

The VKORC1 gene encodes the vitamin K epoxide reductase complex subunit 1, an enzyme involved in the vitamin K cycle and essential for the activation of clotting factors. The G1639A polymorphism in the VKORC1 gene has been associated with variations in warfarin sensitivity and clotting factor activity (48). Studies on the association between the VKORC1 G1639A polymorphism and BRVO have yielded mixed results, with some suggesting a potential link and others finding no significant association (49).

Genetic polymorphisms in endothelial function

Endothelial dysfunction plays a crucial role in the pathogenesis of BRVO. Several genetic polymorphisms affecting endothelial function have been studied, including those in the endothelial nitric oxide synthase (eNOS) gene (40).

Inflammation-related genetic polymorphisms

Polymorphisms in genes encoding inflammatory mediators, such as interleukins and chemokines, have been studied in relation to BRVO. For instance, multiple SNPs in cytokine genes, including IL1 β -511C>T, IL1RN 1018T>C, IL4 -584C>T, IL6 -174G>C, IL8 -251A>T, IL10 -592C>A, IL18 183A>G, CCL5 -403G>A, MCP-1/CCL2 -2518A>G and TNF- α -308G>A, have been investigated. However, these studies have generally not found significant associations between these polymorphisms and BRVO development (50).

Oxidative stress-related genetic polymorphisms

Heme oxygenase-1 (HO-1) is an important antioxidant enzyme that inhibits proinflammatory responses. The HO-1 -413A>T polymorphism has been studied, but no association with BRVO was found. Apolipoprotein E (APOE) also plays a role in oxidative stress and inflammation. The APOE E4 allele is associated with lower plasma APOE levels and increased risk for cardiovascular disease. Although the E4 allele has been impli-

cated in BRVO and non-diabetic retinopathy, recent studies did not find a correlation between the E4 allele and BRVO (51).

Stromal-cell-derived factor 1 (SDF-1) polymorphism

Stromal-cell-derived factor 1 (SDF-1), a member of the C-X-C motif subfamily (also known as CXCL12), plays a key role in the mobilization of hematopoietic stem-cell-derived endothelial progenitor cells, which are essential in retinal neovascularization associated with ischemic retinal diseases. Hypoxia-induced SDF-1 expression in endothelial cells triggers inflammation and compromises the blood-retina barrier, thereby promoting angiogenesis. By binding to its receptor CXCR4, SDF-1 stimulates the release of VEGF, creating a positive feedback loop that further amplifies SDF-1 expression (52).

Studies have shown varied results regarding the association between SDF-1 levels and BRVO. Ki-I *et al* documented higher vitreous SDF-1 levels in patients with RVO complicated by neovascularization compared to those without neovascularization and controls (53). Conversely, Zeng *et al* found comparable CXCL12 vitreous concentrations between RVO patients and control subjects (54). Additionally, Szigeti *et al* reported that the SDF1-3'(801)A allele predisposes individuals to ocular neovascularization as a complication of RVO. Recent research, did not find a significant correlation between the SDF1-3'G(801)A polymorphism and BRVO development (52).

Paraoxonase 1 (PON1) polymorphism

Paraoxonase 1 (PON1) is an enzyme linked to high-density lipoprotein (HDL), enhancing its anti-inflammatory and antioxidant capabilities. PON1 can hydrolyze a range of substrates, demonstrating paraoxonase, lactonase and arylesterase activities, which help inhibit the oxidation of LDL. Its anti-atherogenic properties are largely attributed to its ability to reduce proatherogenic oxidized LDL (ox-LDL), a key factor in foam cell formation (55).

The Q192R SNP is the most extensively researched polymorphism of PON1, influencing the enzyme's activity in a substrate-specific manner. The Q192 variant exhibits higher lactonase and arylesterase activities, while the R192 variant is more efficient at hydrolyzing paraoxon.

The L55M polymorphism, on the other hand, affects PON1 levels without directly altering its enzymatic activity, with the L55 variant being more stable and resistant to proteolysis (50).

Angayarkanni *et al*. found significantly lower PON1-arylesterase activity in CRVO patients compared to controls, implicating oxidative stress and ox-LDL in CRVO (56). A study from Ortak *et al* proposed a protective effect of LL genotype in the L55M polymorphism for RVO pathophysiology, though researchers did not find any effect of Q192R (55). However, it was observed that the LL genotype provided a better response to intravitreal anti-VEGF injections (50). It was also found that carriers of the PON1 192 R allele had a statistically significant increased risk of RVO compared to QQ homozygotes, aligning with previous reports (50). □

CONCLUSIONS

The considerable impact of BRVO on global vision health is unquestionable. As one of the leading causes of vision impairment and the second most common retinal vascular disease leading to blindness, BRVO represents a significant public health challenge (18). Its impact, highlights the critical need for comprehensive strategies that include early detection, modification of risk factors, and targeted treatments to alleviate the associated consequences (57). Ocular factors like glaucoma, uveitis and short axial length emphasize the complexity of BRVO etiology.

Advancements in diagnostic imaging have revolutionized the detection and monitoring of BRVO, with technologies such as FA, OCT and OCT-A providing detailed insights into the retinal vascular pathology. These imaging modalities not only facilitate early diagnosis but also inform the prognosis and guide therapeutic decisions, marking the importance of technological innovation in improving patient outcomes.

Future research should aim to elucidate the genetic and molecular factor for BRVO, explore novel therapeutic targets, and evaluate the impact of lifestyle interventions, ultimately paving the way for personalized medicine approaches in the management of this prevalent and debilitating condition. □

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