THE POTENTIAL ROLE OF NOS1 G-84A POLYMORPHISM IN IGA VASCULITIS

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Abstract: Background: Immunoglobulin A vasculitis (IgAV) is a systemic small-vessel vasculitis characterized by vascular inflammation and endothelial injury. Nitric oxide (NO) is an important regulator of vascular tone and endothelial function. The NOS1 gene encodes neuronal nitric oxide synthase (nNOS), which contributes to NO production in different tissues. Genetic variation in NOS1 may influence NO-dependent vascular regulation.

Objective: To evaluate the potential role of the NOS1 G-84A polymorphism in the pathogenesis of IgA vasculitis, with particular consideration of nitric oxide metabolism and endothelial dysfunction.

Methods: A focused review of available biomedical literature was performed using publications concerning NOS1 G-84A, nitric oxide metabolism, endothelial dysfunction and vascular inflammatory disorders. Particular attention was given to studies investigating the functional consequences of the G-84A variant and its possible relationship with vascular pathology.

Results: The NOS1 G-84A polymorphism is located in a regulatory region of the NOS1 gene. Experimental studies demonstrated that the A allele may reduce promoter activity, suggesting a potential influence on NOS1 expression and NO production. The -84A allele has also been associated with vascular and other pathological phenotypes in several populations. However, direct evidence linking NOS1 G-84A specifically with IgA vasculitis remains limited. Therefore, this polymorphism may be considered a biologically plausible candidate marker for studying endothelial dysfunction in IgAV rather than an established genetic risk factor.

Conclusion: The NOS1 G-84A polymorphism may have potential relevance to IgA vasculitis through its possible effects on NO-dependent vascular regulation. Further case-control studies are required to determine whether this variant is associated with IgAV susceptibility, disease severity or specific clinical manifestations.

Keywords: IgA vasculitis; Henoch–Schönlein purpura; NOS1; G-84A; neuronal nitric oxide synthase; nitric oxide; endothelial dysfunction; genetic polymorphism.

1. Introduction

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch–Schönlein purpura, is the most common systemic small-vessel vasculitis in childhood. The disease is characterized by palpable purpura, gastrointestinal manifestations, joint involvement and, in some patients, renal complications.

Although immune-complex deposition and inflammation are central mechanisms of IgAV, endothelial dysfunction is also considered an important component of vascular injury. Nitric oxide (NO) plays a major role in maintaining vascular homeostasis by regulating vascular tone, platelet activity and interactions between blood cells and the endothelium.

Nitric oxide is synthesized by nitric oxide synthase enzymes. The NOS1 gene encodes neuronal nitric oxide synthase (nNOS), which contributes to NO-mediated signaling. Therefore, genetic variants affecting NOS1 expression may potentially modify vascular responses during inflammatory conditions.

The G-84A polymorphism of NOS1 is of particular interest because it is located in a regulatory region of the gene. Experimental analysis of this variant demonstrated that the -84A allele can decrease promoter activity by approximately 30%, suggesting a functional effect on NOS1 expression.

2. Materials and Methods

A focused literature review was conducted using PubMed/MEDLINE and available international biomedical publications. The search included the terms “NOS1 G-84A,” “NOS1 -84G>A,” “neuronal nitric oxide synthase,” “IgA vasculitis,” “Henoch–Schönlein purpura,” “nitric oxide,” and “endothelial dysfunction.”

Studies investigating the biological function of the NOS1 G-84A polymorphism and its association with vascular or inflammatory disorders were considered.

3. Results and Discussion

The NOS1 gene encodes neuronal nitric oxide synthase, an enzyme involved in the synthesis of nitric oxide. Although NOS1 was initially characterized mainly in the nervous system, NO produced through nNOS-dependent pathways has broader physiological effects, including modulation of vascular tone.

The potential importance of the G-84A polymorphism is supported by functional evidence. In a study investigating the promoter region of NOS1, carriers of the A allele demonstrated approximately a 30% reduction in

promoter activity compared with the wild-type allele. These findings indicate that the G-84A variant may influence NOS1 transcription.

Changes in NOS1 expression may theoretically affect local NO availability. Reduced NO bioavailability can contribute to impaired vascular relaxation, endothelial activation and altered interactions between circulating inflammatory cells and the vascular wall.

Evidence from other vascular diseases also supports the biological relevance of the -84A allele. For example, the NOS1 -84A allele has been investigated in association with vascular disorders, and studies have suggested that this allele may influence disease susceptibility in specific populations.

However, the direct relationship between NOS1 G-84A and IgA vasculitis has not yet been adequately established. Current genetic research in IgAV has focused more extensively on immune-regulatory, inflammatory and endothelial-related genes, while evidence specifically addressing NOS1 G-84A remains limited.

This lack of direct evidence should not necessarily exclude the polymorphism from investigation. IgAV involves inflammatory injury of small vessels, and endothelial dysfunction may contribute to increased vascular permeability and the characteristic clinical manifestations of the disease. Because NOS1 participates in NO-dependent vascular regulation, the G-84A variant represents a biologically plausible candidate for genetic studies of IgAV.

An important advantage of investigating NOS1 G-84A is the possibility of evaluating its interaction with other genes involved in the NO pathway, particularly NOS3. Previous genetic studies in other vascular conditions have demonstrated that NOS1 and NOS3 polymorphisms may interact and influence vascular function.

Therefore, investigation of NOS1 G-84A in IgAV may be particularly informative when combined with clinical phenotyping, including assessment of renal, gastrointestinal and cutaneous manifestations.

4. Conclusion

The NOS1 G-84A polymorphism represents a potentially relevant genetic marker for studying endothelial dysfunction in IgA vasculitis. Experimental evidence indicates that the -84A allele can reduce NOS1 promoter activity, providing a possible molecular mechanism through which this variant may influence NO-dependent vascular regulation.

Nevertheless, current evidence is insufficient to classify NOS1 G-84A as an established genetic risk factor for IgA vasculitis. Its role should therefore be investigated in well-designed case-control studies with adequate sample sizes and detailed clinical phenotyping.

Future research should determine whether the G-84A polymorphism is

associated with IgAV susceptibility, disease severity, gastrointestinal involvement, renal involvement or recurrence, and whether its effects interact with other endothelial and nitric oxide pathway genes.

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