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Case Report

Intravitreal Fluocinolone Acetonide 0.19 mg Implant in a Patient with Resistant Blau Syndrome: A Case Report

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Keywords
Blau syndrome · Choroiditis · Fluocinolone acetonide implant · Immunomodulatory therapy · Uveitis

Abstract
Introduction: Blau syndrome is a progressive disease with an unknown etiology and pathogenesis. It can cause severe damage, especially in the eye with severe involvement. ***Case Presentation:*** A six-year-old female was referred to us complaining about blurry vision and floaters in both eyes for 1 year. She had been diagnosed with Blau syndrome and Blau syndrome-associated anterior uveitis. Her best-corrected visual acuity in the right and left eyes was 20/70 and 20/80, respectively. Slit-lamp exam revealed faint bilateral band keratopathy along with 1+ anterior chamber cells and posterior synechia 360° in both eyes. During dilated fundoscopy, 2+ haze in the media was observed, along with swollen and hyperemic disc OU. Based on changes in optical coherence tomography, fluorescein angiography, and indocyanine green angiography, she was diagnosed with panuveitis and retinal vasculitis. Given her complicated history, we decided to proceed with an intravitreal fluocinolone acetonide 0.19 mg implant implantation in both eyes. During the 1-month follow-up visit, vitreous haze, retinal vasculitis, and active choroiditis were resolved. At 6-month follow-up visit, no changes were observed compared to the 1-month follow-up visit. ***Conclusion:*** In cases of Blau syndrome that display resistance to systemic immunomodulatory therapies, the inclusion of local treatments, such as the intravitreal fluocinolone acetonide 0.19 mg implant, should be considered as an adjunctive therapeutic option.

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Introduction

Blau syndrome (BS) is a rare, chronic, granulomatous, autoinflammatory disease caused by one of many possible autosomal dominant gain-of-function mutations in the NOD2/CARD15 gene [1]. BS typically presents before the age of 4 years [2]. It is characterized by the classic triad of a skin rash, arthritis, and uveitis [1]. Typically, the cutaneous and articular symptoms appear prior to the age of 4 years, while ocular symptoms appear between the ages of 7 and 12 years [2]. The estimated incidence of BS in the Danish population is 0.05 per 100,000 per year [2]. This hereditary condition shares common characteristics with juvenile sarcoidosis [3]. The majority of individuals impacted by this condition typically experience polyarticular tenosynovitis (96%) and develop a fine, scaly erythematous rash (80%) during infancy. Other extra-triad manifestations may be large vessel vasculitis, interstitial lung disease, interstitial nephritis, hepatic granulomata, splenomegaly, and erythema nodosum [4].

In patients with BS, uveitis starts with a recurrent, subtle, bilateral, granulomatous anterior uveitis which can evolve to panuveitis with chronic multifocal choroiditis [3]. The involvement of the eyes presents the most significant aspect in terms of morbidity and functional impact [5]. Similar to other pediatric uveitis entities, the diagnosis may experience delays due to various factors, which include challenges in effectively communicating with and examining young children. Morbidities associated with BS-associated uveitis encompass conditions such as cataracts, glaucoma, and amblyopia. Furthermore, the side effects of treatments can impact the child and impose a significant burden on their family.

This case report details a challenging instance of BS featuring panuveitis, where the patient's ocular condition had been underdiagnosed; however, eventually, it was diagnosed with complete paraclinical evaluation and effectively managed through the implantation of a 0.19 mg intravitreal fluocinolone acetonide implant in addition to aggressive immunomodulatory therapy.

Case Report

We received a referral for evaluation of bilateral chronic anterior uveitis in a six-year-old female. She was subjectively complaining about blurry vision and floaters in both eyes for 1 year. She had been diagnosed with BS when she was 19 months old. Anterior uveitis had been first diagnosed when she was 5 years old. She was on frequent topical cycloplegics and corticosteroids in both eyes for her uveitis. Systemically, she was taking mycophenolate mofetil 250 mg twice a day, tofacitinib 4 mg daily, and prednisone 9 mg daily. Additionally, she was receiving infliximab at a dose of 10 mg/kg monthly. She had already failed naproxen, methotrexate, etanercept, tocilizumab, canakinumab, rilonacept, anakinra, golimumab, and intravenous immunoglobulin because of their ineffectiveness or adverse effects. She had also received cyclophosphamide pulse therapy which had been stopped due to aseptic meningitis. Her best-corrected visual acuity (BCVA) in the right (OD) and left (OS) eyes was 20/70 and 20/80, respectively. Intraocular pressure (IOP) was 17 and 18 mm Hg OD and OS, respectively. Slit-lamp exam revealed bilateral faint band keratopathy, along with 1+ anterior chamber cells, posterior synechia 360°, fibrous membrane on lens, and cortical and posterior subcapsular cataract in both eyes (OU) (Fig. 1a, b). During dilated fundoscopy, 2+ haze in the media was observed, along with swollen and hyperemic disc OU (Fig 1c, d). Optical coherence tomography (OCT) of macula showed normal structure and contour OU along with vitreous opacities OD and possible choroidal thickening OU (Fig. 2a, c). Optic nerve head OCT retinal nerve fiber layer thickness map demonstrated thickening of retinal nerve fiber layer OU (Fig. 3a, c). Fluorescein angiography (FA) depicted disc and vascular leakage in both eyes (Fig. 1g, h). Indocyanine green angiography showed hypocyanescent lesions OU with indistinct borders, indicating active choroiditis OU (Fig. 1k, l).

Based on the involvement of the retina, retinal vessels, optic nerve, and choroid, we diagnosed her with bilateral panuveitis and retinal vasculitis OU. Given her complicated history, we decided to proceed with intravitreal fluocinolone acetonide 0.19 mg implant implantation OU after discussing the risks and benefits with her parents instead of waiting for a successful systemic remedy by pediatric rheumatologists. During the 1-month follow-up visit, floaters had disappeared. The BCVA OD and OS was 20/50 and 20/40, respectively, and IOP was 20 and 21 mm Hg OD and OS, respectively. Figure 1e and f illustrate improvement seen in media haziness and disc swelling on dilated fundoscopy, the stability of OCT of macula OU along with no vitreous opacities OD, improved choroidal thickening OU (Fig. 2b, d), improvement in the optic nerve OCT (retinal nerve fiber layer) (Fig. 3b, d), FA (Fig. 1i, j) and indocyanine green angiography with transition from active choroiditis and granuloma into distinct choroidal scars (Fig. 1m, n).

At 6-month follow-up visit after intravitreal fluocinolone acetonide 0.19 mg implant implantation, her BCVA was 20/30 and 20/25 OD and OS, respectively, IOP was 19 mm Hg OU, and no changes were objectively observed, including cataract progression compared to the 1-month follow-up visit. Written informed consent was obtained from the mother of the patient for publishing the details of her medical case and any accompanying images. The CARE Checklist was completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535984).

Discussion

BS is a progressive disease with an unknown etiology and pathogenesis, although some genes have been identified [6]. Frequently, it is misdiagnosed or undiagnosed as a result of its low frequency and clinical characteristics. Thus, it can cause severe damage, especially in the eye with severe involvement [6]. Studies have demonstrated that 32% of patients diagnosed with BS experience significant visual impairment, which affect the quality of life for both BS patients and their families [7]. Thus far, no established therapeutic approach has been identified for the treatment of BS. Due to the uncommon nature of the disease, the current treatment approach relies on anecdotal evidence from case reports and small case series. The primary objective of treatment is to mitigate the risk of blindness and minimize joint deformity [6].

As we mentioned earlier, there are no established guidelines for the treatment of BS. While high doses of systemic corticosteroids are necessary during acute phases of disease, it is advisable to pursue steroid-free immunomodulatory therapy for long-term management, particularly in young patients to minimize the potential side effects associated with systemic corticosteroid therapy.

Conventional immunomodulatory therapy agents such as methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil are the first line of steroid-free therapy [8]; however, TNF-α inhibitors are currently the prevailing treatment option for patients with BS. Nevertheless, in cases where their effectiveness is limited, alternative medications should be considered [6]. These medications include IL-1 and IL-1β inhibitors such as canakinumab [9], IL-6 inhibitors such as tocilizumab [6], intravenous human immunoglobulin (0.4 g/kg/month) [10].

There have also been some novel treatments, including antibiotics (minocycline, doxycycline, and clarithromycin) [10] and thalidomide (less than 25 mg daily) [8]. However, these agents have been examined in case reports, and further, robust studies are required to substantiate these treatments.

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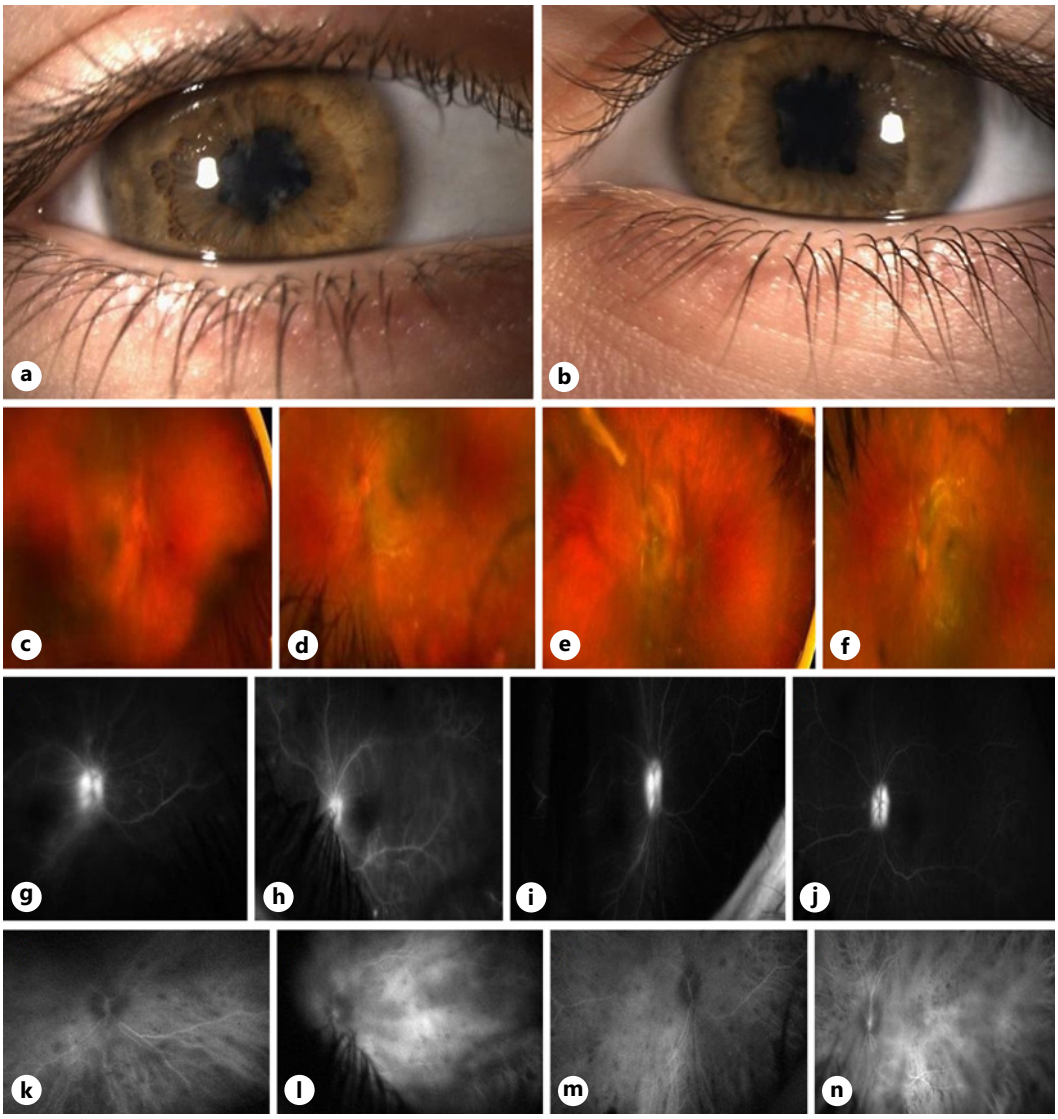

Fig. 1. a, **b** External images of right eye (OD) and left eye (OS), respectively, at the first visit which reveal faint band keratopathy nasal and temporal of cornea OD and temporal of cornea OS, posterior synechia 360 degrees, fibrous membrane on lens, and cortical and posterior subcapsular cataract in both eyes (OU). **c**, **d** Fundus photos of OD and OS, respectively, at the first visit which show hazy media and disc swelling OU. **e**, **f** Fundus photos of OD and OS, respectively, at the 1-month follow-up visit which demonstrate no media haziness and improvement in disc swelling in OU. **g**, **h** Fluorescein angiography (FA) of OD and OS, respectively, at the first visit which depict disc and vascular leakage in both eyes. **i**, **j** FA of OD and OS, respectively, at the 1-month follow-up visit which show impressive improvement in disc and vascular leakage in both eyes. There is still staining of optic nerve head OU secondary to papilledema. **k**, **l** Indocyanine green angiography (ICGA) of OD and OS, respectively, at the first visit which show hypocyanescent lesions OU with indistinct borders indicating active choroiditis OU. **m**, **n** ICGA of OD and OS, respectively, at the 1-month follow-up visit which show hypocyanescent lesions OU with more distinct borders indicating distinct choroidal scars of previous active choroiditis OU.

Despite attempting all the aforementioned medications, including escalated doses and one cycle of cyclophosphamide pulse therapy, our patient's eyes exhibited no response. Considering that the ocular involvement significantly impacts morbidity and functional impairment in patients with BS, we opted to proceed with intravitreal fluocinolone acetonide 0.19 mg implant

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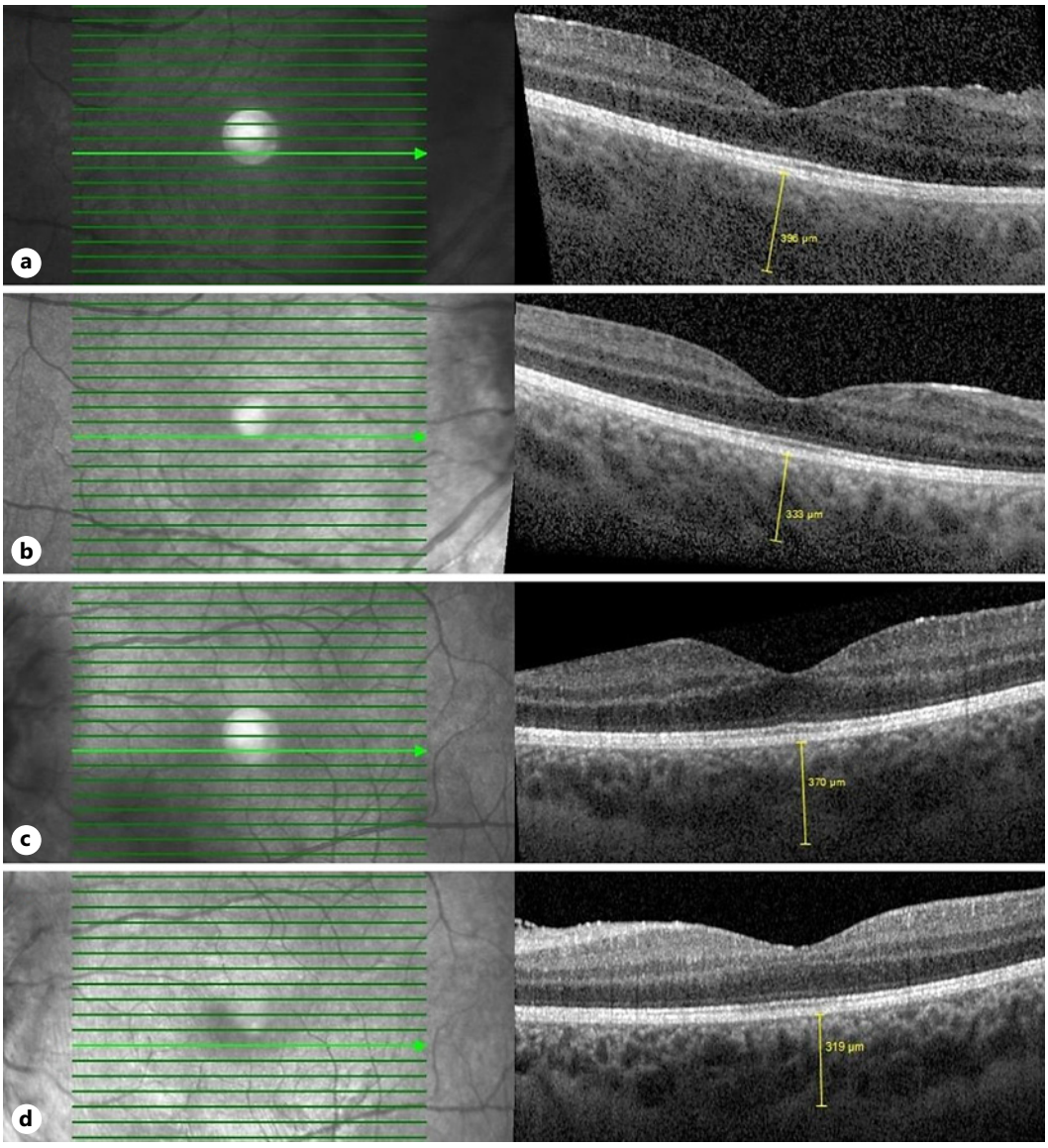

Fig. 2. a Optical coherence tomography (OCT) of right macula (OD) at the first visit which shows normal structure and contour, along with vitreous opacities and possible choroidal thickening (395 µm). **b** OCT of macula OD at 1-month follow-up visit which shows resolved vitreous opacities and improved choroidal thickening (333 µm). **c** OCT of left macula (OS) at the first visit which shows normal structure and contour, along with possible choroidal thickening (370 µm). **d** OCT of macula OS at 1-month follow-up visit which shows improved choroidal thickening (319 µm).

implantation in both eyes. During 1-, 3-, and 6-month visits, the patient remained stable, and she no longer reported blurry vision or floaters. FA at 1 month indicated the absence of active inflammation in the retinal vessels, optic nerves, and macula. However, optic nerves exhibited staining in FA due to papilledema, a condition that the patient had been previously diagnosed with (Fig. 1i, j). Additionally, at the 1-month (Fig. 1m, n) and 6-month follow-up, ICG revealed distinct choroidal scars with no signs of additional active choroiditis or choroidal granuloma.

We might face criticism for administering triamcinolone acetonide 0.19 mg instead of the specifically approved 0.18 mg for noninfectious panuveitis. However, at the time of treating this case, only triamcinolone acetonide 0.19 mg was available at our facility. Furthermore,

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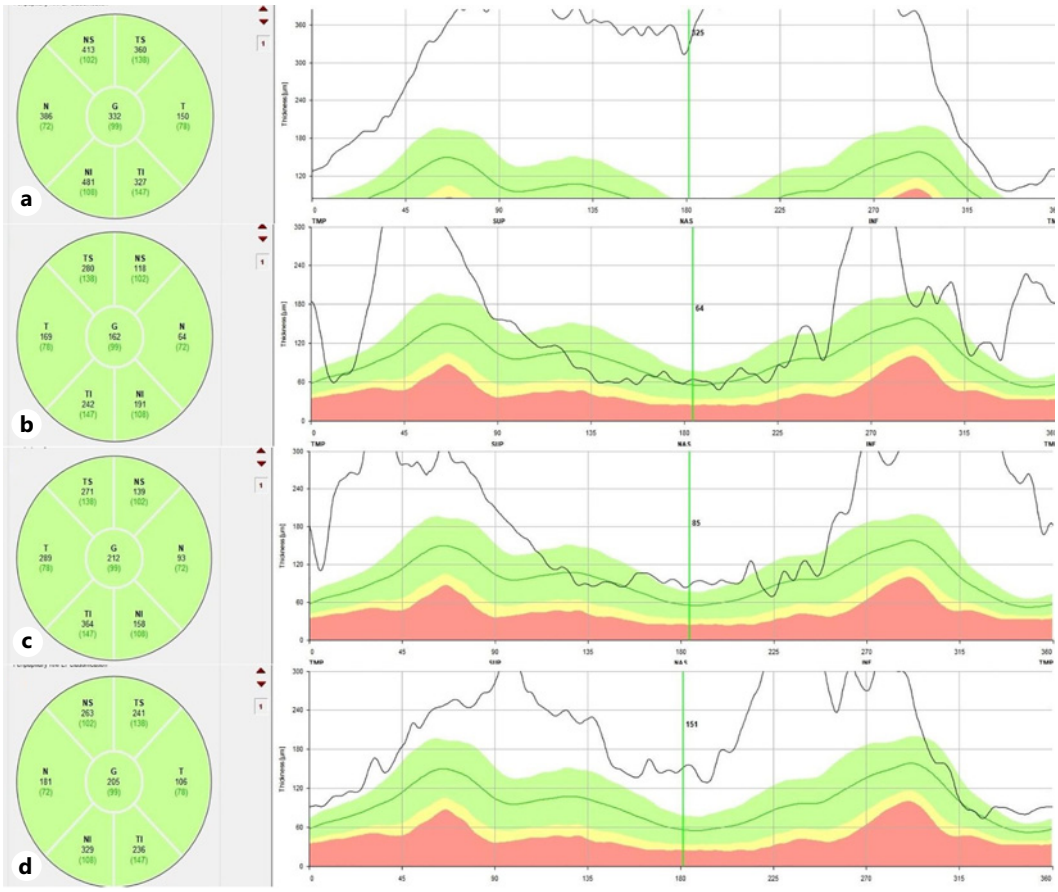

Fig. 3. Circular optical coherence tomography (OCT) of optic nerve head. **a** Segmentation of retinal nerve fiber layer (RNFL) and RNFL thickness map in the right eye (OD) at the first visit which shows thickening of RNFL. **b** Segmentation of RNFL and RNFL thickness map OD at the 1-month follow-up visit which shows an improvement in the thickening of the RNFL. **c** Segmentation of RNFL and RNFL thickness map in the left eye (OS) at the first visit which shows thickening of RNFL in the superior and inferior quadrants. **d** Segmentation of RNFL and RNFL thickness map OS at the 1-month follow-up visit which shows an improvement in the thickening of the RNFL.

there is a wealth of supporting evidence in various reports regarding the efficacy of triamcinolone 0.19 mg in treating uveitis and uveitic macular edema [11, 12]. Additionally, this does not change the idea of local therapy in resistant cases. We may also be criticized for employing local therapy in a patient with severe systemic disease. Although we do agree with this idea, we maintain that local therapy is a reasonable approach in resistant cases with BS to avoid more ocular morbidities. This is because persistent inflammation in the eyes can lead to irreversible damage and, subsequently, visual impairment. Our patient already had ocular morbidities at the time of presenting to us. While it is acknowledged that local steroids can lead to glaucoma and cataracts, it is essential to note that these potential side effects can be effectively managed through vigilant monitoring and the application of appropriate medical and surgical interventions. The condition of the lens and IOP in our patient remained unchanged throughout the follow-up period, extending up to 6 months. It is essential to highlight that she had been receiving regular topical cycloplegic and corticosteroid treatments in both eyes before the intravitreal triamcinolone 0.19 mg implantation. These medications were discontinued after intravitreal triamcinolone implant implantation.

Conclusion

Comprehensive investigation with ancillary testing, including OCT of the macula and optic nerve head, FA, and ICG, is essential for delineating the extent of eye involvement in BS. In resistant cases of BS, the addition of local therapy such as intravitreal fluocinolone acetonide 0.19 mg implant should be taken into consideration as an adjunct therapy.

Statement of Ethics

Ethics approval was not required in accordance with local guidelines and the University of Florida Intuitional Review Board. Written informed consent was obtained from the mother of the patient for publication of the details of the medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Arash Maleki and Khushi Saigal: conception and design of the study, data analysis and interpretation, drafting of the manuscript, and approval of the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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