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# Macular Edema in Childhood Uveitis

## Makulaödem bei kindlicher Uveitis

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### Key words

pediatric uveitis, macular edema, vision loss, complications, intraocular inflammations, pediatric ophthalmology

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### ABSTRACT

**Background** Pediatric uveitis is associated with a high incidence of severe and frequently permanent visual loss. This article summarizes the current understanding of the disease and the therapeutic options that are available to improve treatment outcomes.

**Methods** A Medline search spanning the last 10 years was undertaken using the key terms “pediatric uveitis” or “childhood uveitis” and “macular edema”. Articles which appertained to case reports or small case series were excluded from consideration, whereas those in which the opinions of experts were expressed, as well as reviews, were not. The information contained in these latter two forms of publication was particularly valuable, owing to the scarcity of prospective clinical data appertaining to the treatment of pediatric uveitis-associated macular edema.

**Results** Ten years ago, 34% of children who presented with uveitis manifested secondary complications at the time of diagnosis. During the ensuing 3 years of treatment, this rose to 86%. Heightening awareness of the disease with earlier referrals to expert centers, as well as the advent of therapeutic strategies involving anti-TNF agents and intravitreal corticosteroids, have led to a decrease in the incidence of legal blindness in the affected eyes from 18–69% to below 8% during a five-year course of treatment.

**Conclusion** Early diagnosis and strict control of inflammatory activity have led to a dramatic reduction in the incidence of vision-threatening secondary complications. In the majority of cases, it has also been possible to resolve cystoid macular edema, which, if insufficiently controlled by systemic therapy, usually responds well to intravitreal dexamethasone implants.

### ZUSAMMENFASSUNG

**Hintergrund** Das Risiko eines schweren und bleibenden Sehverlustes ist bei kindlicher Uveitis besonders hoch. In diesem Artikel werden deshalb die der schlechten Prognose zugrunde liegenden Mechanismen und die modernen Behandlungsmöglichkeiten dargestellt, mit denen sich erstaunlich gute Langzeitresultate erreichen lassen.

**Methoden** Grundlage für diese Übersicht bildet eine Medline-Suche mit den Suchbegriffen „pädiatrische Uveitis“ oder „kindliche Uveitis“ und „Makula-Oedem“. Unter den Artikeln der letzten 10 Jahre wurden Fallberichte und kleine Fallserien ausgeschlossen; Übersichtsartikel mit Expertenmeinungen wurden berücksichtigt, da kaum prospektives Datenmaterial zur Behandlung der kindlichen Uveitis und des mit ihr vergesellschafteten entzündlichen Makulaödems existiert.

**Ergebnisse** Bis vor 10 Jahren zeigten 34% der Kinder bereits bei der Diagnosestellung Sekundärkomplikationen ihrer Uveitis. Trotz Behandlung stieg der Anteil an Augen mit Sekundärkomplikationen im Verlauf von 3 Jahren auf 86% an. Ein verbessertes Problembewusstsein und die frühere Überweisung der Kinder an spezialisierte Zentren hat einen früheren Einsatz moderner immunmodulierender Therapien, insbesondere Biologika und intravitrealer Depotsteroiden, ermöglicht, wodurch das Risiko eines Visusabfalls der betroffenen Augen auf unter 0,1 von 18–69% auf unter 8% gesunken ist.

**Schlussfolgerungen** Eine frühzeitige Diagnose und konsequente Behandlung der kindlichen Uveitis haben zu einer erstaunlichen Reduktion der Häufigkeit von Sekundärkompli-

kationen geführt. Fast immer gelingt es, ein entzündliches Makulaödem zu kontrollieren, wenn bei nicht ausreichendem Ansprechen auf die systemische immunmodulierende Thera-

pie auch intravitreale Dexamethason-Implantationen eingesetzt werden.

## Introduction

Children comprise 5–10% of the uveitis population, with anterior affections being the most common. In these young patients, the differential diagnostic spectrum differs from that in adults. Uveitis is more frequently diagnosed in the latter than in the former. The difficulty that is experienced in diagnosing the disease early and the higher prevalence of the chronic condition may contribute to the limited visual prognosis in children [1–5]. On the other hand, owing to the characteristic clinical picture, a specific etiology is more frequently established in children than in adults (71% versus 55%, respectively) [6].

However, the therapeutic options for children are limited, since, owing to the lack of prospective clinical data, the range of approved and tolerated drugs is more restricted. Consequently, the incidence of severe vision loss is high and frequently permanent [7]. In this article, the relative merits of the available therapeutic options in improving the long-term outcomes of treatment are reviewed.

## Methods

Towards the close of June 2017, a Medline search spanning the past 10 years was undertaken using the key terms “pediatric uveitis” or “childhood uveitis” and “macular edema”. Amongst the 33 articles that were thereby retrieved, those involving case reports and series of fewer than ten patients were excluded from consideration, whereas publications in which the opinion of experts was expressed, as well as reviews, were not. The information that was gleaned from the latter two forms of publication was all the more valuable in that prospective clinical data appertaining to pediatric uveitis-associated macular edema is so scarce. The articles were weighed on the basis of their informational pertinence to the focus of the present study.

## Results

In cases of anterior uveitis, juvenile rheumatoid arthritis (JIA) is the most frequently diagnosed specific etiology. Intermediate uveitis is not linked to an underlying systemic condition and is idiopathic in most instances. It accounts for about a quarter of all cases of uveitis in children. In these young patients with intermediate uveitis, the leading cause of visual impairment is cystoid macular edema, whereas in those with a posterior affection, it is toxoplasmosis. Panuveitis is encountered, but rarely in children. Nevertheless, when it does occur, the clinical course is usually severe, as after the spreading of a previously undiagnosed posterior uveitis or a presenting sign of a systemic affection, such as sarcoidosis or pediatric Behçet’s disease. Finally, masquerade syndromes, including retinoblastoma, leukemia and the presence of foreign bodies,

have to be considered in atypical cases that fail to respond to systemic therapy [5–10].

In children, uveitis is bilateral in 40–75% of the cases [1, 3, 4]. In 18% of cases, the visual acuity lies below 0.1 [2]. Even if the patients have good vision at the time of presentation, the risk of visual loss at a future date is nevertheless high, owing to the existence of secondary complications in a high proportion of the eyes (more than one-third) already at this juncture. Interdisciplinary efforts to establish the etiology of the disease are necessary for the instigation of a targeted therapeutic strategy. This must aim at completely controlling any inflammatory activity and reducing the risk of vision loss in these young patients. Hence, even under treatment with topical steroids and methotrexate, an average of 4.2 complications per patient have been demonstrated to develop in 86% of a cohort of 148 eyes during the course of 3 years (► Fig. 1) [4]. In cases of anterior uveitis, band keratopathy, cataracts, and posterior synechiae are frequently associated with JIA [11]. In children with intermediate or panuveitis, macular edema is frequently present and is associated with visual loss, which may have existed for a considerable time before the diagnosis is made and which, owing to the presence of amblyopia, may limit the functional prognosis [4]. Unless a child’s general state of health is particularly poor, the high tolerance of functional impairments and compensatory mechanisms may contribute to delays in presentation and thus in the diagnosis of uveitis. These factors are compounded by the typically insidious onset of the disease, which, unlike adult forms of acute anterior uveitis, is not heralded by a hot and painful eye [1, 8]. The first symptom that draws the attention of parents is squinting [12].

In 2009, the National Institutes of Health (NIH) in the USA reported on a series of children with uveitis, which was associated with macular edema in many instances [8]. At this time, no biologicals had as yet been approved for ophthalmic use. The disease was therefore treated by the administration of an immunosuppressive agent, namely, methotrexate, cyclosporin A, or mycophenolate, which fail to bring the condition under control in one-third of the cases. Although this therapeutic approach does not meet with general approval, the use of biological therapies in children is in some instances the only viable option [13, 14]. Indeed, when it is instigated in a timely manner, it meets with great success, with a drop in the rate of legal blindness from 69.6% (under therapy with corticosteroids, methotrexate, or cyclosporin A) [4] to below 20% (► Fig. 2) [8], a reduction of CME (cystoid macular edema) by 50%, and the need for intraocular surgery from 45.9% [4] to 18.9% [8]. This is also supported by the outcomes of two other series of cases of pediatric intermediate uveitis. In these, 20% [15] and 64% [16] of the children, respectively, presented with macular edema, many of whom the visual acuity was very poor. Five years after treatment with conventional immunosuppressive agents, the visual acuity improved significantly, but was still not satisfactory (0.4). In cases of pediatric uveitis-associated

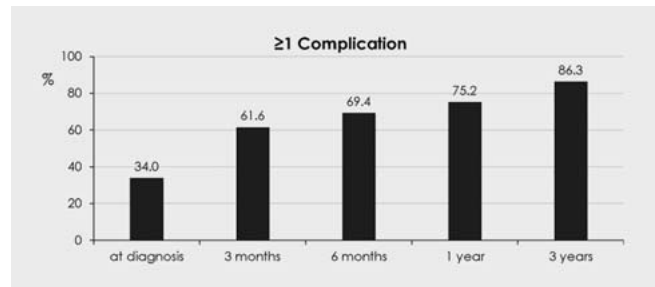
macular edema, the ophthalmologist is confronted with a dilemma in so far as the actual condition is not so aggressive as to warrant treatment escalation indispensable if long-term visual losses are not taken into account. If a minor degree of permanent macular edema is accepted, the visual acuity would drop to 0.4 or less after 5 years under conventional immunosuppressive therapy, which nowadays would be considered as unacceptable [15, 16]. Consequent treatment, including biological agents, guided by regular clinical disease activity assessments as well as noninvasive OCT (optical coherence tomography) examinations to quantify the change in central retinal thickness, if macular edema is present [17, 18], would lead to an inactivation of the disease in 75% of cases after 3 years [19]. Considering that 50–95% of the children suffer from bilateral affection and 75% from a chronic course, this therapy may go along with a dramatic improvement in life quality and perspectives in these patients [20–22]. Of crucial importance is the juncture at which the therapy is initiated, which should be before the disease has become chronic and before permanent tissue damage has been induced [19].

Whereas intravitreal triamcinolone may be a cost-effective option for the treatment of CME in children, it is frequently associated with relevant side effects of cataract progression and an uncontrolled intraocular pressure [23]. The intravitreal injection of a single dose of dexamethasone in cases of pediatric uveitis is highly effective in bringing the disease activity under control. In many instances, this treatment modality can be instigated without the risk of inducing cataract formation and secondary glaucoma, whereas if two to three injections of dexamethasone are administered, these untoward side effects have to be reckoned with [24–26]. Nevertheless, compared to the induction of amblyopia, they are lesser evils.

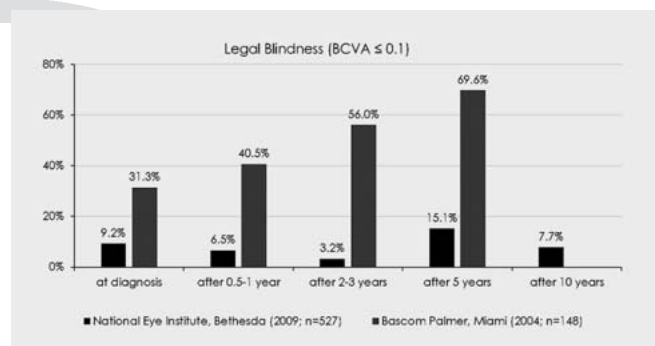
## Discussion

If an eye, namely in a pediatric patient, does not adequately respond to systemic corticosteroid or immunomodulatory therapy within 3 months of treatment onset, a therapy escalation including biological agents is strongly recommended and may result in an inactive disease in up to 75% [19] and remission in 21% of instances [27]. Based on the available therapeutic evidence and excellent safety profiles, the use of biological therapies has to be considered early despite the absence of an approval for this treatment in children by the national health authorities because of the strong impact on daily tasks [20–22]. Disease awareness beyond general ophthalmologists and pediatricians as well as an early referral to specialized uveitis centers, if the disease activity is incompletely controlled, is a prerequisite to improve outcomes [22, 28, 29]. Nevertheless, contraindications have to be considered, including active and latent bacterial infections and immune-pathological and immuno-oncological diseases in disposed individuals [30].

If all of the systemic therapeutic options do not completely resolute disease activity and inflammatory macular edema, then intravitreal therapies are worth consideration [24–26]. Their application in children, however, requires general anesthesia so that topical options are worth consideration. Beyond these, difluprednate, a topical steroid, has demonstrated good efficacy in child-



► **Fig. 1** Even in the face of treatment with methotrexate and topical corticosteroids, the incidence of complications increases in proportion to the duration of the disease activity (source of data: [4]).



► **Fig. 2** Changes in the visual prognosis of treatment for pediatric uveitis during the past decade (source of data: [4, 8]).

hood uveitis as an adjuvant to systemic immunomodulatory therapy. Beyond 25 eyes, 88% demonstrated an at least two-step improvement in inflammatory activity and 78% an improvement in CME, but for the price of a severe rise in the intraocular pressure in 50% and cataract progression in 39% [31]. Although it is an FDA-approved drug, the costs of its use in Switzerland are not covered by health insurance companies except in exceptional cases, owing to its great expense (320 CHF per vial, which would suffice for the full treatment of a single patient over 4–6 weeks). Hence, the financial situation should be clarified before embarking on a course of therapy with this agent. If the disease activity cannot be brought under control medically, or if traction is manifested, then it will be necessary, also in children, to resort to surgery, which is indeed an effective measure. After vitrectomy with removal of inflammatory debris, disease activity can be abated in 75 to 80% of the cases [18, 32, 33].

In conclusion: Typically, in cases of pediatric uveitis, presentation is late and is urged on by the rearing up of secondary complications. By this time, the prognosis for a satisfactory outcome of treatment is poor with conventional immunomodulatory therapy. If the condition is not then aggressively handled onwards, the risk of a long-term loss of vision is high, with an 18% incidence of legal blindness. Even in the face of therapy, the incidence of complications increases in proportion to the duration of the disease activity. Hence, every effort should be made to bring the condition under control at the earliest possible juncture, without delay, after

the diagnosis has been established. The prevention of new complications encountered under therapy and the absence of macular edema have to be set as markers for long-term therapeutic success and as predictors for functional stability. Although the risk of a severe long-term loss of vision is ever present, it can be reduced by a careful consideration of all of the available therapeutic options, including biologicals and intravitreal corticosteroids. Depending on the nature of the underlying disease, remission rates of 21 to 37% can be achieved.

### Conflict of Interest

J. G. G. acts as an advisor to several pharmaceutical companies and contributes to a number of clinical investigations. These activities had no bearing on the study that underlies the submitted manuscript. The author received neither direct nor indirect financial support for the investigation and he has no conflicting interests with the presented data.

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