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RISK FACTORS FOR GLAUCOMA SURGERY IN CHILDHOOD UVEITIS

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ABSTRACT

Purpose: To identify risk factors for medically uncontrollable high intraocular pressure (IOP) secondary to uveitis in children.

Methods: Patients diagnosed with uveitis before their 18th birthday and with a minimal follow-up of one year were included from the ophthalmology departments of the University Medical Center Groningen and the University Medical Center Utrecht in a retrospective case-control study.

Results: A total of 196 patients were included, 85 of whom had undergone glaucoma surgery (cases). Compared to those without glaucoma surgery (controls), cases were younger (median age 6 versus 8 years, P=0.008), uveitis was more often located anteriorly (78% versus 62%, P=0.02) and was predominantly associated with juvenile idiopathic arthritis (JIA) (62% versus 35%, P<0.001). During follow-up, cases underwent cataract surgery more often (80% versus 31%, P<0.001), had higher maximum IOPs (median IOP 37 mmHg versus 27 mmHg, P<0.001), and more often used > 2 types of glaucoma medication (83% versus 24%, P<0.001). Of those needing > 2 types of glaucoma medication 68% underwent glaucoma surgery within one year. Gender, bilaterality, visual acuity and ocular complications at diagnosis, ANA positivity, use of systemic immune-suppression, and cataract surgery before glaucoma surgery were not significantly different between the two groups. Cox survival analysis showed that anterior uveitis (P = 0.04) and increased IOP at presentation (P = 0.02) were predictive of increased risk of needing glaucoma surgery.

Conclusion: Anterior location of the uveitis and higher IOP at presentation are associated with an increased risk of glaucoma surgery. Patients who need > 2 types of glaucoma medication are likely to need glaucoma surgery, usually within 1 year after increasing the number of medications.

INTRODUCTION

The most common causes of vision loss in childhood uveitis are cataract, band keratopathy, glaucoma and cystoid macular edema[1,2]. The reported prevalence of secondary glaucoma in children with uveitis ranges between 5 – 25 %[1–4] and IOP elevation in childhood uveitis has been reported to range between 3–51%[3].

Secondary glaucoma occurs when uveitis is associated with elevated intraocular pressure (IOP) and optic nerve damage, resulting in irreversible visual field loss. Damage of the trabecular system due to inflammation, but also the topical steroids used as treatment of uveitis can increase the IOP. Secondary glaucoma in childhood uveitis has an unpredictable course, with large IOP fluctuations, varying responses to eye-pressure lowering medication, and a frequent steroid-response[5]. Increased IOP is initially treated pharmacologically in a stepladder approach. If after these pharmacological steps IOP is still unacceptably high, glaucoma surgery is required. To obtain the best long-term visual outcome, it is important to identify the children who are at increased risk for the development of secondary glaucoma at an early stage and to treat them by glaucoma surgery before irreversible damage has occurred[6].

Two previous studies on risk factors for secondary glaucoma reported a female preponderance, juvenile idiopathic arthritis (JIA) as the most common etiology, and anterior uveitis as predictive anatomical site for developing ocular hypertension or glaucoma in children with uveitis[7,8]. Heinz et al show a significantly higher need for glaucoma surgery in childhood uveitis compared to uveitis in adults[8]. A study to identify risk factors for the need of glaucoma surgery in medically uncontrollable raised IOP secondary to childhood uveitis has not yet been performed.

The aim of this study is to identify risk factors of raised IOP needing glaucoma surgery in childhood uveitis. For this purpose, we evaluated a large group of children with uveitis and compared those who needed surgery to those who did not. Identification of such factors may contribute to the early detection of the need for glaucoma surgery in this patient group, thus enabling surgery at an early stage of the disease and the prevention of irreversible damage.

PATIENTS AND METHODS

Patients diagnosed with uveitis before their 18th birthday and with a minimal follow-up of 1 year were included from the departments of ophthalmology of the University Medical Centers of Groningen (UMCG, the Netherlands) and Utrecht (UMCU, the Netherlands). Patients were diagnosed with uveitis between 1989 and

2016 and were identified from the uveitis databases of both centers. The Medical Ethical Committee of the UMCG and UMCU approved the conduction of the study. All the patients needing glaucoma surgery ("cases") from both centers were included. The control group ("controls") consisted of all patients without glaucoma surgery from the UMCG, whereas for the UMCU cohort one random patient not needing glaucoma surgery was used as a control for each patient needing glaucoma surgery. Data collection was done from the ophthalmological medical records.

Uveitis diagnosis

The diagnosis of uveitis was made by ophthalmologists specialized in childhood uveitis. Classification of uveitis was done according to the Standardization of Uveitis Nomenclature (SUN) criteria[9] and was based on the available information in the ophthalmological medical records. Children were evaluated for the presence of an underlying systemic disease by pediatric rheumatologists. Activity of anterior chamber (AC) inflammation (cells) evaluated by standard slit-lamp examination was recorded according to the recommendations of the SUN working group[9]. Cells in the vitreous were scored as being present or not. The diagnosis of posterior and panuveitis was made by fundoscopy and on indication fluorescein angiography (FA) was performed.

Glaucoma diagnosis

The assessment of necessity for glaucoma surgery was done by ophthalmologists specialized in glaucoma and was based on a combination of intraocular pressure level, the number of different types of glaucoma medication, and IOP-related irreversible changes to visual field or optic nerve.

We analyzed the data of one eye per patient. In the surgery group, if both eyes underwent glaucoma surgery, the eye that first underwent surgery was used. In the control group, if the uveitis was bilateral, the eye with the first presentation of uveitis was used. If both eyes were affected at the same time, the worst eye with regards to visual acuity, complications and IOP at diagnosis was chosen. When both eyes were equally affected a random eye was chosen.

General descriptives

The following information was recorded: age at onset of uveitis, gender, classification of uveitis, anti-nuclear antibodies (ANA) status, ocular complications at presentation, surgical procedures and systemic medication. Intra-ocular pressure and anti-glaucoma medication were recorded at regular intervals during follow-up until glaucoma surgery or in the control group until the last ophthalmic examination. IOP at disease remission was measured when observable inactive disease for longer than 3 months was documented, with a maximum daily maintenance dosage of local steroids of 3 times per day, with or without systemic immunosuppressive medication.

Ocular complications

Complications were scored as anterior when band keratopathy, cataract, or posterior synechiae were present. Posterior complications were scored when macular edema or papillitis were present. All patients needing cataract surgery during follow up were recorded. Additionally, as possible risk factor for glaucoma surgery, cataract surgery > 3 months prior to glaucoma surgery was recorded.

Visual acuity

The decimal equivalent of the Snellen visual acuity (VA) of the affected eyes was recorded at presentation. The Snellen VA was converted to logarithm of the minimum angle of resolution units (LogMAR) VA for calculations.

Data analysis

Data were statistically analyzed with SPSS 23.0.0 (SPSS Inc, Chicago, Illinois, USA). A $P<0.05$ was considered statistically significant. Bonferroni correction was applied where needed. Descriptive statistics were used to present mean and standard deviation (SD) in normally distributed data or median and inter quartile range (IQR) in non-normally distributed data. In case of non-normally distributed linked samples, the Wilcoxon test for paired samples and the Mann-Whitney U test for independent samples were used. For the differences between the nominal data groups we used the Chi-square test. A Cox survival analysis was performed. All categorical variables were dichotomized for the purpose of this analysis. The need for glaucoma surgery was defined as the event. Covariates present at baseline with $P\leq0.2$ were analyzed as predictors in a backward stepwise conditional method. To correct for differences in data between the two centers, we added the center as a covariate to the multivariable model. The survival curve was graphically displayed as mean value for all covariates. In one covariate, 20% of the data-points were missing. Missing data patterns were analyzed and the data was classified as missing at random (MAR) based upon Little's MCAR test (supplementary data: Table 2). Missing data was compensated for by imputing mean values (supplementary data: Table 2). Next to that, analyses were repeated with missing data compensated by multiple imputation and outcomes were compared to original data and data with imputed values (supplementary data: Table 2, 3)[10,11].

RESULTS

Patients characteristics are summarized in Table 1. In total 196 patients (85 female) were included in the study. In the univariable comparisons, cases were younger than the controls (median age 6 versus 8 years, $P=0.008$).

Table 1. Characteristics complete cohort

	Total (n=196)	Glaucoma surgery (cases, n=85)	No glaucoma surgery (controls, n=111)	P-value
Number of patients	196	85	111	
Median age at uveitis onset (yrs), (IQR)[b]	7 (4-10)	6 (4-9)	8 (5-11)	**0.008**[a]
Center 1[c]	97 (49%)	34	63	
Center 2[d]	99 (51%)	51	48	
Gender – female	85 (43%)	53	32	0.51[e]
Bilateral disease	134 (68%)	57	77	0.73[e]
Anatomic location uveitis (n (% of total))				**0.02**[e]
Anterior	135 (69%)	66	69	
Intermediate	21 (11%)	6	15	
Posterior	8 (4%)	0	8	
Pan uveitis	32 (16%)	13	19	
Median LogMar visual acuity at diagnosis (IQR)	0.22 (0.11 to 0.60)	0.22 (0.03 to 0.60)	0.22 (0.01 to 0.70)	0.61[a]
Ocular complicatons (n (% of total))[f]				0.11[c]
No complications	56 (29%)	24	32	
Anterior complications[g]	66 (34%)	36	30	
Posterior complicatons[h]	36(18%)	11	25	
Anterior and posterior complications	36(18%)	14	22	
Etiology (n (% of total))				**< 0.001**[c]
E.c.i	81 (41%)	28	53	
JIA[i]	92 (47%)	53	39	
HLA-B27	6 (3%)	3	3	
infectious	11 (6%)	1	10	
Other auto-immune	6 (3%)	0	6	
ANA[j] positive	104 (57%)[i]	53 (62%)	51 (46%)	0.07[c]
IOP[l] **measurements** (mmHg), (median, (IQR))				
First IOP measurement	16 (13 - 20)	16 (14 - 22)	16 (13 - 19)	0.11[a]
IOP disease remission	19 (15 - 23)	21 (17 - 27)	18 (15 - 21)	**0.002**[a]
Highest IOP during FU[m]	32 (24.5 - 38)	37 (34 - 42)	27 (20 - 32)	**< 0.001**[a]
Time measurements (months, (median, (IQR))				
Time to disease remission[n]	6 (3 - 12)	5 (3 - 10)	6 (3 - 14)	0.23[a]
Time to highest IOP during FU[o]	17 (6 - 41.5)	28 (10 - 52)	13 (3 - 36)	**0.004**[a]
Time to start glaucoma medication	6 (1 - 21)	5 (1-21)	9 (1-25)	0.33[a]
Time to glaucoma surgery	N/A[p]	31 (12-54)	N/A[p]	
Median FU	86 (43 - 144)	114 (71 - 180)	66 (37 - 115)	**< 0.001**[a]
Additional treatment (n (% of total))				
Systemic immune- suppression				
At start uveitis[q]	71 (36%)	24	47	**0.04**[c]
During follow up[r]	160 (82%)	71	89	0.47[c]
Cataract surgery	102 (52%)	68	34	**< 0.001**[c]
Cataract surgery before glaucoma surgery[s]	65 (33%)	31	34	0.39[c]
Maximum glaucoma medication used (n)	5	4 (4 - 5)	1 (0 - 2)	**< 0.001**[a]
> 2 types of glaucoma medication n (% of total))	107 (54%)	83	24	**< 0.001**[c]

[a] Mann-Whitney, [b] interquartile range,[c] Center 1 = University medical center Groningen. From this center, all cases and controls were included. [d] Center 2= University medical center Utrecht. All cases were included and 48 randomly chosen controls were included. [e] Pearson chi-square, [f]missing n=2, [g]anterior complications: *Band keratopathy*, *cataract*, *posterior synechiae*, [h] posterior complications : *Macular-edema*, *papillitis*, [i]Juvenile idiopathic arthritis, [j]Anti nuclear antibodies, [k] missing n=12, [l] IOP = intra ocular pressure, [m] FU = follow up, [n]missing n=42, [o]missing n= 2, [p] N/A = not applicable, [q]missing n=1, [r] missing n=2,[s] cataract surgery longer than 3 months before glaucoma surgery

Anterior location of the uveitis and JIA related uveitis were significantly more frequently present in the cases (78% versus 62%, P=0.02 and 62% versus 35 %, P<0.001), respectively). At presentation, anterior ocular complications tended to be more frequently observed in the cases, but this difference was not statistically significant (59 % versus 47 %, P=0.1). ANA-positivity tended to be, although not statistically significant, more frequently found in the cases (62% vs 46%, P=0.07). The cases used more often more than two different types of glaucoma medication during the follow-up (83% versus 25%, P<0.001) and 70% of the cases underwent glaucoma surgery within 1 year after increasing the number of glaucoma medication to three or more types (Table 2).

Table 2. Cumulative number of patients operated for glaucoma[a]

Time to surgery	Number (%) of patients [b]
< 1 year	58 (70%)
< 2 years	65 (78%)
< 3 years	72 (87%)
< 4 years	77 (93%)
< 5 years	79 (95%)
< 6 years	80 (96%)

[a] Cases using more than two types of glaucoma medication are displayed. In the controls 24 patients used more than two types of glaucoma medication. [b] In 3 cases data on time to glaucoma surgery are missing and 2 cases used ≤ 2 types of glaucoma medication

Median (IQR) follow up time overall was 86 (43–144) months with a longer follow up time in the cases (P<0.001). Overall, cataract surgery was performed more frequently in the cases (67% vs 31%, P<0.001). If only cataract extractions performed >3 months prior to glaucoma surgery were included in the analysis, no differences were found between cases and controls.

Patient data differed between centers. The total cohort of patients included from the UMC Utrecht (Center 2) as compared to the UMC Groningen (Center 1) were younger (P=0.04), had more frequently a JIA-related uveitis (P=0.02), had more frequently an anterior uveitis (P=0.005) and less patients suffered from posterior complications (P=0.001). Cox proportional hazards regression analysis was used as a predictive model for time-to-event data. After accounting for the confounding effect of center, we found that anterior uveitis (HR 2.1 (95% CI 1.0 to 4.2); P=0.04) and higher IOP at presentation (HR 1.05 per mmHg (95% CI 1.0 to 1.1); P=0.02) were independently and significantly associated with a higher risk of glaucoma surgery (supplement data: Table 3). A survival curve was graphically displayed for the mean of covariates in the entire patient group (Figure 1).

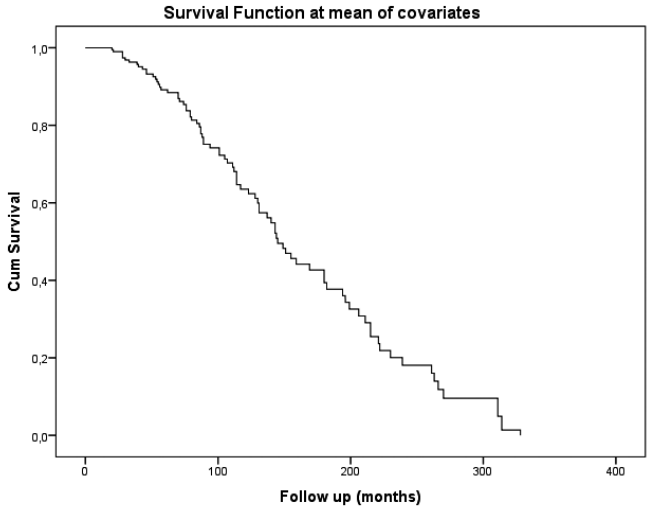

Figure 1. Survival-curve at mean covariates for the entire patient group. The relationship between the influence of multiple risk factors on the probability of glaucoma surgery is displayed for the entire patient group. The horizontal axis shows the time to glaucoma surgery, the vertical axis shows the probability of survival. The shape of the survival function is estimated from all observed subjects.

DISCUSSION

In this study with 196 pediatric uveitis patients, we show that the risk of glaucoma surgery is highest in children with anterior uveitis. Our data also indicates that in the majority of the cases glaucoma surgery is required within a year after a third type of glaucoma medication is prescribed. In patients with uveitis onset at younger age, JIA-related uveitis and patients with higher IOP during follow up, statistically significantly more glaucoma surgery is performed. Known risk factors from the literature such as ANA positivity, female predominance and anterior complications[12], are not confirmed in our study.

In our multivariate Cox survival analysis, after adjusting for other covariates, only anterior uveitis and IOP at diagnosis are independently and significantly associated with a higher risk of glaucoma surgery. Anterior uveitis is a known risk factor for the development of ocular hypertension and glaucoma[7,8,12–15]. Also, for the treating ophthalmologist, anterior uveitis is a clearly identifiable risk factor, whereas IOP at presentation is much less clinically relevant, since median IOP (16 mmHg) did not differ between the cases and controls. Although anterior uveitis is most frequently found in the cases, the presence of anterior complications at diagnosis such as band keratopathy, cataract, or posterior

synechiae are not related to a higher risk of glaucoma surgery in our study (P=0.1), which contradicts the literature[7,8,12–15].

During follow-up, additional risk factors were identified by univariable analyses (Table 1). Of these, requirement of a third type of glaucoma medication can be considered as a tipping point, since it indicates the need of glaucoma surgery within a year in the majority of the cases. (Table 2). More frequent monitoring of IOP and compliance to glaucoma medication are recommended for these children. Also, early referral to an ophthalmologist specialized in glaucoma-surgery is advised to prevent a delay in surgical treatment of glaucoma.

In our study, patients who require glaucoma surgery are younger at the time of uveitis diagnosis. This may indicate a more severe disease and inherent complications due to prolonged disease and treatment with topical steroids[13,16]. There is no consensus in the literature regarding this aspect, since some previous studies agree[8,13], but others report older age at onset of the uveitis to be related to ocular hypertension or secondary glaucoma[12].

More patients with JIA-uveitis were found among the cases when compared to the controls (53 (58%) vs 39 (42%), P=<0.001). In the literature, the prevalence of glaucoma in JIA-associated uveitis has been reported to range from 14 -40%[12]. JIA-related uveitis is most commonly anteriorly located, chronic and most patients are treated in a uveitis expertise center. We included patients from two tertiary centers, of which the UMCU is an academic expertise center for patients with JIA. This possibly explains the relatively higher need of glaucoma surgery in the JIA subgroup when compared to the literature[7,13].

In our study, topical, subconjunctival as well as systemic anti-inflammatory medication are widely used mostly during the whole follow-up. Increasing IOP due to steroid-response induced by topical steroids may therefore play an important role, despite the careful prescription of local steroids and a maximum daily maintenance dose of 3 times per day. In children, the ocular-hypertensive response to topical steroids occurs more frequently, severely and rapidly than in adults[1,17,18]. Elevation of IOP can be found in most patients as early as the first or second week[19,20]. In our study, the highest IOP during the follow-up is measured after 28 months in the surgery group and 13 months in the control group with a large variation in time. This relatively late increase in IOP in both groups is a combined result of changes in the trabecular system, the ocular-hypertensive response to topical steroids, and adaptations in glaucoma medication during follow-up. Thus reflecting the multifactorial pathophysiology of increasing IOP in uveitis.

In some papers, previous cataract surgery is related to the severity of the uveitis and a higher risk of uveitic glaucoma[12,16]. In our data, the proportion of cases that underwent cataract surgery before glaucoma surgery was not statistically significantly different from that of controls. During the entire follow-up, more cataract surgery is performed in the cases than in the controls (68% versus 34%, P<0.001). The development of cataract is probably based on the impact of glaucoma surgery and the long-term use of medication to control the uveitis[19,21].

To analyze the differences between the two groups at diagnosis and in the course of the disease, we followed the patients as long as possible. The follow-up is shorter in the controls when compared to the cases, partly because of a loss to follow-up due to a stable course and therefore a return to the referring ophthalmologist. With a different follow-up duration in cases versus controls of 9 years versus 6 years, it is likely that there are patients in the control-group who will need glaucoma surgery in the future.

Various surgical techniques are possible for treating glaucoma in childhood[22,23]. Glaucoma surgery is still a challenge for the ophthalmologist and far-reaching for the child. In this patient group, it is essential to perform surgery on time, but choosing the optimal moment is difficult. Weighing the chance of irreversible visual loss due to glaucomatous damage against that from complications induced by glaucoma surgery are difficult considerations[22]. The changes in eyesight, uncertainty about the disease course, necessary changes in medication and frequent school absence due to monitoring visits to the ophthalmologist may have a strong impact on the quality of life of a young patient and their parents[24]. Finding a balance between prevention of irreversible loss of vision due to glaucoma and reducing the iatrogenic impact on a child's quality of life is a challenge encountered in all cases.

In our study, we combined data from the UMCG and the UMCU. Our cox-regression analysis showed a significant differences between the two centers (supplement data: Table 3). This differences are meanly based on differences in patient population, due to the specialized health care in treating JIA patients at the UMCU and the responsibility for specialized and more general care of uveitis patients during the study period at the UMCG.

The results of the current study are limited by the fact that the study is retrospective, there is a large variability in follow up time and data-imputation was performed for variables with missing data. All patients were included from two tertiary centers in the Netherlands and therefore do not represent the total spectrum of pediatric uveitis. Also, personal experience or preferences of ophthalmologists and pediatric rheumatologist may have influenced the choice and course of treatment. The strengths of this study are its cohort size,

the systematic way in which data were collected, its adherence to the SUN classification system and guidelines for publications[9–11] and the sharing of expertise in a difficult and challenging patient population.

CONCLUSION

This study on the risk factors for developing medically uncontrollable high intraocular pressure in pediatric uveitis is one of the largest currently available in the literature. The authors emphasize the importance of careful treatment and monitoring in pediatric uveitis patients with anterior uveitis, JIA-related uveitis and in patients who are already treated with more than two types of glaucoma medication. Adequate monitoring, risk assessment and early referral to a glaucoma specialist experienced in this patient group is recommended.

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Supplement data: Table 1. Variables with ≥ 10% missing data

Missing (n(% of total)	Total	Center 1	Center 2	P-value[a]	Cases	Center 1	Center 2	P-value[a]	Controls	Center 1	Center 2	P-value[a]
First IOP measurement	40 (20%)	23	17	0.2	18	7	11	0.9	22	16	6	0.09
IOP disease remission	39 (20%)	22	17	0.3	22	8	14	0.6	17	14	3	**0.02**
Time to disease remission	42 (21%)	24	18	0.2	23	10	13	0.7	19	14	5	0.1

[a] Pearson chi-square

Supplement data: Table 2. Imputed data[a]

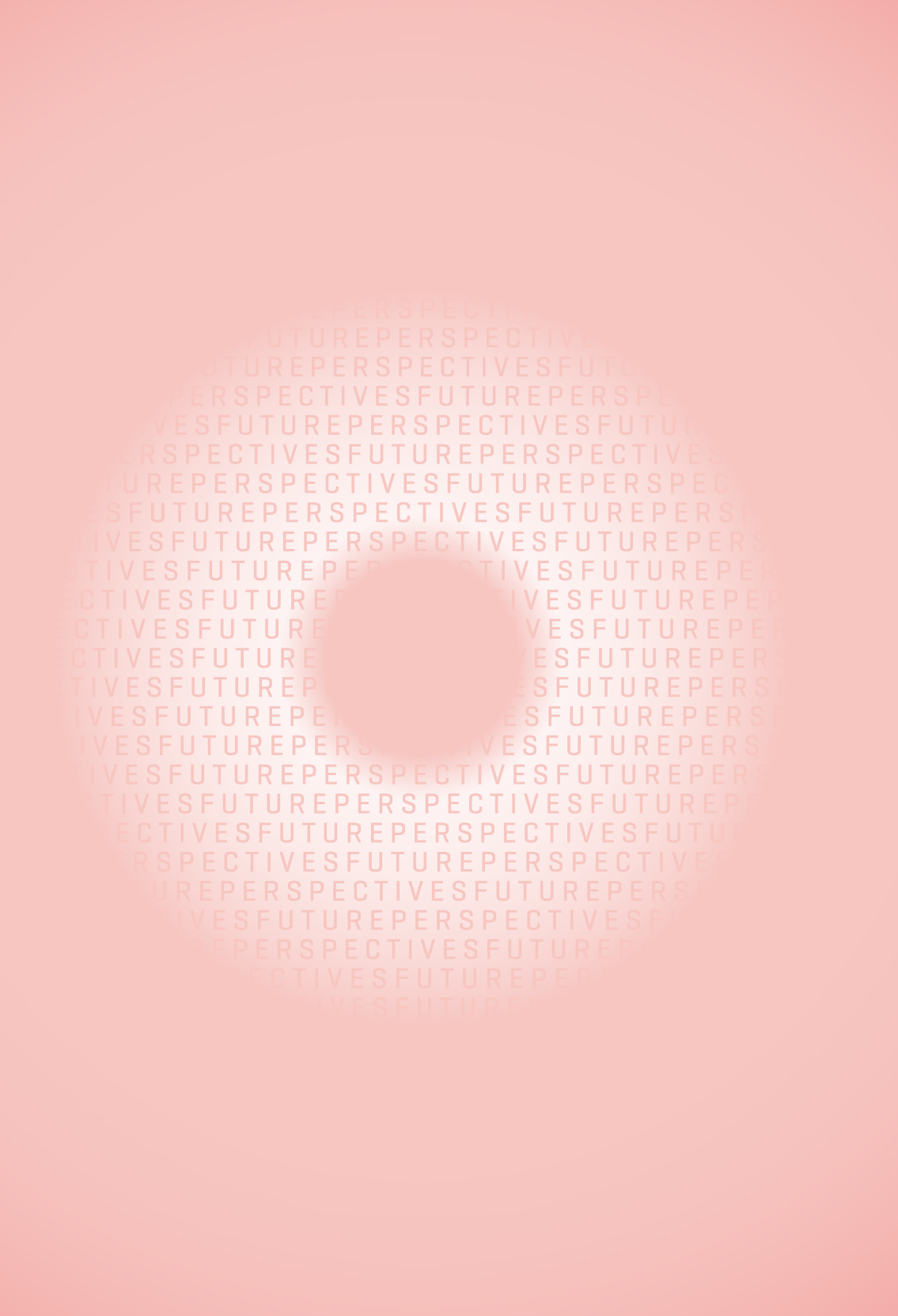
Variables	Original data (mean, SD)	Pooled data (mean, SEM)
First IOP measurement (mmHg)	16.9 (± 6.1)	16.9 (0.5)
IOP disease remission (mmHg)	19.9 (± 7.7)	20 (0.6)
Time to disease remission (months)	9 (± 9)	9.5 (0.7)

[a] Multiple imputation by Linear Regression. Missing data was missing at random (MAR) (Little's MCAR test: P =0.006). Thirteen cases with missing data on all three variables were excluded from data-imputation. Variables with missing data on < 3 variables were used as predictors for imputation. Constraints were set based upon observed minimum and maximum values found within the variables. Number of imputations: 20.

Supplement data: Table 3. Outcome Cox-regression analysis in original and imputed data. P-value < 0.1[c]

Variables[c]	Original [a]	1[b]	2[b]	3[b]	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[b]	11[b]	12[b]	13[b]	14[b]	15[b]	16[b]	17[b]	18[b]	19[b]	20[b]	21[d]
Center	0.04	0.04	0.04	0.02	0.02	0.06	0.03	0.04	0.05	0.03	0.02	0.04	0.06	0.02	0.02	0.04	0.03	0.03	0.02	0.04	0.02	0.02
Age at onset uveitis (yrs)			0.09	0.06	0.06		0.06				0.06			0.06			0.09	0.07	0.05		0.06	
Anterior location uveitis	0.02	0.06	0.08			0.09		0.06	0.05	0.08		0.06	0.08		0.05	0.06						0.04
JIA																						
ANA																						
Anterior complications																						
First IOP measurement (mmHg)	0.02	0.005	0.07	0.005	0.05	0.003	0.02	0.003	0.06	0.01	0.05	0.05	0.005	0.02	0.002		0.02		0.07	0.01	0.09	0.02

[a] Original database, [b] Imputed dataset, [c] Variables with significance level P < 0.1 are presented, [d] Mean imputed.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