Etiologies of Chronic Anterior Uveitis at a Tertiary Referral Center over 35 years.

Andrea D. Birnbaum,[1] Deborah M. Little[1-3], Howard H. Tessler[1], Debra A. Goldstein[1]

1. University of Illinois at Chicago Department of Ophthalmology and Visual Sciences
2. University of Illinois at Chicago Departments of Neurology and Rehabilitation Medicine
3. University of Illinois at Chicago Department of Anatomy and Cell Biology

Corresponding Author:

Andrea D. Birnbaum

University of Illinois at Chicago Department of Ophthalmology and Visual Science

1855 West Taylor

Chicago, IL 60612

Introduction

Anterior uveitis is the most common diagnosis at uveitis referral centers in countries across the world.[1-15] By far, the most common diagnosis in this group of patients is "idiopathic" anterior uveitis.[1-4, 8,9,11-14] Anterior uveitis refers to inflammation that is primarily located in the anterior chamber (iritis) or in the anterior chamber and anterior vitreous (iridocyclitis). Chronic uveitis has recently been defined as inflammation characterized by prompt relapse (in less than 3 months) after discontinuation of therapy (SUN) Prior to this definition, the term "chronic" had been used to describe inflammation of more than 6-9 weeks duration.[24] Chronic anterior uveitis (CAU) has been associated with non-infectious systemic inflammatory conditions such as sarcoidosis, juvenile idiopathic arthritis (JIA), and tubulo-interstitial nephritis and uveitis syndrome (TINU), as well as systemic infections, such as syphilis and tuberculosis.

Over the past 35 years, improved imaging studies have allowed clinicians to better diagnose certain conditions, such as sarcoidosis.[16-18] Anterior uveitis secondary to TINU has been described.[19] An understanding of the etiology of certain types of uveitis has also expanded, such as the association between Fuchs heterochromic iridocyclitis (FHI) and infection with the rubella virus.[20-22] The relationship between uveitis and a family history of inflammatory bowel disease (IBD) has been described.[23] It is unclear, however, whether these advances have translated into more accurate diagnoses of patients with (CAU) and a resultant decrease in the proportion of these patients given a diagnosis of idiopathic disease. In this study, we describe the trends in diagnosis of CAU over 35 years at the University of Illinois Uveitis Service, with particular focus on newly described etiologies.

Materials and Methods

Study Population

We were granted permission from the Institutional Review Board at the University of Illinois to retrospectively review existing medical records of patients evaluated by the Uveitis Service at the University of Illinois at Chicago between 1973 and 2007 with a diagnosis of chronic CAU. Classification of uveitis was based on Hogan and Kimura's

classification until approximately 1987.[24] After this the modifications of the international uveitis study group were adopted.[25] In 2005, the classification schema of the standardized uveitis nomenclature (SUN) workshop were adopted.[26] For this study, patients were only included if they met the SUN criteria for chronic disease. All patients classified before 2005 had their charts reviewed. In each case, inflammation had persisted for longer than 3 months.   In other words, regardless of date seen, all included patients had chronic inflammation involving the anterior chamber and/or anterior vitreous that persisted for greater than 3 months.

Patients with fundus abnormalities were excluded, except for those with cystoid macular edema (CME), disc edema or subtle venous sheathing. Patients with active occlusive vasculitis or leakage on fluorescein angiography were excluded. All patients were tested for syphilis with a specific treponemal test, and the majority of patients underwent testing for tuberculosis with either a tuberculin skin test or Quantiferon Gold (QFT-G; Cellestis, Ltd., Carnegie, Australia). Patients who were diagnosed with specific entities, such as juvenile idiopathic arthritis or a spondyloarthropathy did not necessarily undergo testing for tuberculosis. Diagnostic criteria for each of the diagnoses are listed in Table 1.

Diagnosis	Criteria – in patients with chronic anterior uveitis
Idiopathic	No known cause identified
Fuchs heterochromic iridocyclitis (FHI)	Clinical diagnosis: Fine stellate keratic precipitates, anterior chamber and anterior vitreous cell, anterior iris stromal atrophy, absence of posterior synechiae, absence of other cause for uveitis.
Sarcoidosis	*Definitive*: Positive biopsy
	Presumed: Bilateral hilar adenopathy, elevated serum angiotensin converting enzyme (ACE) and/or lysozyme
Juvenile idiopathic arthritis (JIA)	Diagnosis by pediatrician or pediatric rheumatologist, elevated antinuclear antibody (ANA), presence of joint disease.
Syphilis	Positive FTA-ABS or comparable test, improvement with intravenous penicillin
Inflammatory bowel disease (IBD)*	Systemic diagnosis of IBD or family history of IBD in first-degree relative
Spondyloarthropathies	Positive HLA-B27, rheumatologic diagnoses: ankylosing spondylitis, reactive arthritis, psoriatic arthritis
CIC of childhood	Elevated antinuclear antibody (ANA) and absence of joint disease.
Sympathetic ophthalmia	Bilateral granulomatous iridocyclitis after perforating trauma (including surgery)
Behcet's disease	Recurrent oral ulcers plus 2 other findings: recurrent genital ulcers, ocular inflammation, skin lesions, positive pathergy test.
Multiple sclerosis (MS)	Neurologic diagnosis of MS
Herpes simplex virus and Herpes zoster virus	History of herpetic infection; clinical findings of elevated intraocular pressure, diffuse KP; posterior pigment epithelial atrophy of iris; positive PCR for viral DNA from aqueous or vitreous sample.

Conditions described in 4 or fewer patients over 35 years:	*Endophthalmitis* (endogenous or exogenous)
	Kawasaki's disease –diagnosis by primary care physician
	Bartonella – positive serum titers
	Takayasu's disease – diagnosis by primary care physician
	Posner-Schlossman – elevated intraocular pressure with inflammation, normal intraocular pressure between attacks, unilateral involvement
	Lyme disease – positive serum titers
	TINU – elevated urine β-2 microglobulin, bilateral anterior uveitis
	Irvine Gass – Cystoid macular edema associated with ocular inflammation after cataract surgery
	CIC after Vogt-Koyanagi-Harada (VKH) – bilateral iridocyclitis without disc edema, sunset glow fundus and multiple chorioretinal scars, vitiligo, alopecia or poliosis
	Malignancy – masquerade syndromes – diagnosed by primary care physician or by anterior chamber cytology
	   • Leukemia
	   • Leukocytoclastic vasculitis
	   • Lymphoma
	   • Acute myeloid leukemia (AML)
	   • Chronic lymphocytic leukemia (CLL)

All diagnoses of chronic anterior uveitis in patients evaluated between 1973-2007 and the diagnostic criteria are listed.
*Family history of IBD was grouped with personal history of IBD based on published literature[23]

Data analysis

Demographic information was calculated based on recorded age at presentation to the Uveitis Service. Many of the records of patients evaluated during the 1970s and 1980s listed only race and clinical findings, but did not include age at presentation. The relative frequency of each diagnosis of chronic anterior uveitis was calculated (SPSS, Chicago, IL, USA) and plotted (Sigma Plot, San Jose, CA, USA). Linear regression analysis was performed on diagnoses comprising at least 5% of total CAU cases. Separate analyses were then performed on adult and pediatric (<17 years) patients. A combined analysis was performed for diagnoses making up less than 1% of all patients in order to determine whether the combination of uncommon diagnoses changed significantly over time.

Diagnoses making up less than 1% were then grouped into decades, and the frequency of each diagnosis per decade was calculated. Herpetic eye disease included that due to both herpes simplex and zoster. Inflammatory bowel disease (IBD) included those patients with either a personal or family history of the disease, when information on family history of IBD was provided.

Results

Between 1973 and 2007, a total of 5970 new patients were evaluated by the Uveitis Service at the University of Illinois. Thirty-one percent (n=1855) of these patients were diagnosed with chronic anterior uveitis. The average age at presentation was 42 years, with a range of 2 to 93 years. A total of 213 pediatric patients (ages 2 to 16 years) were included in this cohort, representing 13.3% of the CAU patients with known age at presentation (n=1598). Data were not available on exact age at presentation for many of the patients who were initially evaluated between 1973 and 1987. The majority of patients were female (69.6%). The racial distribution was divided among Caucasian (45.8%), African American (34.9%), Hispanic (6.8%), and Asian (3.6%) patients.

Idiopathic disease was diagnosed in 53.6% of patients with CAU over the course of the study (n=994), with Fuchs heterochromic iridocyclitis (FHI), sarcoidosis (presumed and biopsy-proven), and juvenile idiopathic arthritis (JIA) each also comprising over 5% of total patients. The diagnoses made in ≥ 1% of patients are shown in Table 2. Tubulo-interstitial nephritis and uveitis (TINU) was diagnosed in 6 patients between 2003 and 2007; Lyme disease was the etiology in only 2 patients between 2002 and 2007. Diagnoses given to less than 1% of patients with CAU are included in Table 1 but not repeated in Table 2.

Etiology	Frequency (n)	Percent of Total
Idiopathic (granumolatmous and non-granulomatous)	994	53.6
FHI	223	12.0
Sarcoidosis	259	13.9
• *Presumed*	*210*	*11.3*
• *Biopsy-proven*	*49*	*2.6*
Juvenile idiopathic arthritis (JIA)	113	6.1
Spondyloarthropathies	62	3.3
Syphilis	51	2.7
Multiple sclerosis (MS)	30	1.6
IBD	23	1.2
HSV	18	1.0
HZV	18	1.0

Table 2. Etiology of Chronic Anterior Uveitis. The etiology of chronic anterior uveitis for all diagnoses making up at least 1% of patients are shown.

Idiopathic CAU had a 9% decrease in frequency of diagnosis over time, as measured by linear regression (p<0.04) (Figure 1A). This decrease was more pronounced (approximately 13%) when the adult population was analyzed separately, (p<0.003) (Figure 1B), and an approximately 3% increase was measured in the pediatric subgroup (< 17 years) (p<0.04) (Figure 1C).   No significant change in frequency was measured for sarcoidosis by regression analysis (p<0.548) (Figure 2A). The data however were not normally distributed. The data collected for FHI showed a bimodal distribution. As such, although linear regression was performed and did not show a significant change in diagnosis over time, the accuracy of such findings are

limited (Figure 2B). The relative frequency of JIA (Figure 2C) did not show a statistically significant increase (p<0.067), although a trend was noted. These 4 diagnoses comprised 85% of all patients with CAU, with idiopathic disease continually accounting for greater than 39% of cases. A final regression analysis was performed in which all diagnoses aside from idiopathic disease, sarcoidosis, FHI and JIA were grouped together. No significant change in frequency of diagnosis was measured in this combined group over time (p=0.187) (Figure 2D).

When the less common diagnoses were grouped by decade, CAU secondary to herpetic disease (simplex and zoster) did not show a dramatic change over time. HLA-B27-associated disease showed an increase of 2.6% between 1995 and 2004 versus 1975 to 1984. Inflammation related to a personal or elicited family history of inflammatory bowel disease showed an even greater increase of 3.3% during the same time period, while disease related to multiple sclerosis showed an increase of 1.0%. Syphilis, on the other hand, showed a decrease of 4.1% (Table 3).

Etiology	1975-1984	1985-1994	1995-2004
n (per decade)	362	552	686
Herpetic uveitis	4 (1.10%)	10 (1.81%)	11 (1.60%)
HLA-B27 uveitis	7 (1.93%)	21 (3.80%)	25 (4.53%)
Inflammatory bowel disease	3 (0.83%)	7 (1.27%)	23 (4.17%)
Multiple sclerosis	5 (1.38%)	11 (1.99%)	13 (2.36%)
Syphilis	19 (5.25%)	16 (2.90%)	8 (1.17%)

Table 3. Frequencies of less common causes of chronic anterior uveitis, grouped by decade. The less common etiologies of chronic anterior uveitis that presented between 1975 and 2004 were grouped by decade in order to demonstrate the change over time. The greatest increase in frequency over time was measured in patients with a personal or family history of inflammatory bowel disease, while the greatest decrease was noted in patients with chronic anterior uveitis secondary to syphilis.

 Discussion

Chronic anterior uveitis is the most common diagnosis made by the Uveitis Service at the University of Illinois, comprising over one-third of all new patients seen each year. There is a significant literature focused on frequency of anterior uveitis,

including acute, acute recurrent, and chronic disease.[1-15] Values reported are quite variable, representing 18 to 92% of patients, depending on the study. Fewer studies analyze the frequency of chronic anterior uveitis, with reported values between 11 to 26% of patients.[1,4, 27] The higher proportion of patients with chronic disease in this study may be due to the tertiary referral nature of the UIC uveitis service.

This study reveals a small but statistically-significant decrease in the frequency of idiopathic chronic anterior uveitis over the past 35 years. One contributing factor may be better recognition of subtle intermediate and posterior uveitis with improvements in ophthalmoscopy since the 1970s. Interestingly, the frequency of diagnosis of sarcoidosis, FHI and JIA have not significantly increased. This suggests that the decrease in idiopathic disease is not be related to serum diagnostic tests for evaluation of sarcoidosis that have become part of our armamentarium in recent decades, including angiotensin converting enzyme (ACE) and lysozyme.[17,18,28] If these tests had played a role in the decreased diagnosis of idiopathic anterior uveitis, an increase in the proportion of patients with sarcoidosis would have been expected.

In addition to laboratory testing, patients with anterior uveitis often undergo imaging studies as part of their evaluation. These modalities have become more readily available in recent years, leading to an increase in the number of chest x-rays and computerized tomography (CT) studies performed on this population to assess for sarcoidosis and tuberculosis. As with the laboratory tests for sarcoidosis, the addition of chest imaging does not appear to have contributed to the small decrease in idiopathic disease seen at our institution over time. The diagnoses that are supported by findings on chest imaging have either shown no change in frequency over time (sarcoidosis) or were not described in our patients (tuberculosis). Again, an increase in the proportion of patients with sarcoidosis and tuberculosis would have been expected if these imaging studies had played a significant role in the overall decrease in diagnosis of idiopathic disease.

Another possibility that exists, particularly in the case of sarcoidosis, is that the diagnosis is now being made at nearby institutions. Whereas many of these patients might have been referred at least for diagnostic purposes, comprehensive ophthalmologists may have a better awareness of ocular sarcoidosis and may have

become more comfortable diagnosing sarcoidosis on the basis of clinical exam, serum laboratory findings and imaging studies.

It has been hypothesized, based on testing of aqueous humor, that FHI is related to infection with the rubella virus.[21,22] This has been supported by epidemiological data reporting a decreased incidence of FHI in patients born in the United States after 1957, as these were the patients targeted by the rubella vaccination program.[20] In this study, which looks only at the year each patient presented with disease, a bimodal distribution is noted (Figure 2A). The increase in cases of FHI during the 1970's and 1980's with a steady decrease since the late 1990's reflects the initiation of the rubella vaccination program in the United States in 1969 and presentation of FHI during the 3rd and 4th decades of life.[29,30]

During this same period, the trend toward an increase in cases of uveitis related to juvenile idiopathic arthritis (JIA) was calculated to be approximately 3.5%. This increase in JIA cases may have contributed to the overall decrease in relative frequency of idiopathic disease, as the percentage of cases with JIA almost doubled over 35 years. Of note, approximately one third of our patients with JIA presented to our service as adults (17 years or older), which may explain the lack of an inverse relationship between idiopathic CAU in children and JIA. Interestingly, a study in Finland reported an increase in incidence of juvenile rheumatoid arthritis in 1995 compared to values in 1980, 1985, and 1990. They suggested that this variation may be due to environmental factors that trigger the disease in susceptible individuals.[31] Our observed increase may also reflect changes in referral patterns to our institution, as many of the pediatric rheumatologists in the city began refering directly to our service approximately 10 years ago.

The combination of conditions comprising less than 5% of CAU showed a trend toward an increase in frequency of diagnosis, although this did not reach statistical significance. When these same conditions were grouped by decade and analyzed individually, some interesting observations were noted (Table 3). Anterior uveitis related to herpetic eye disease showed only slight variability (within 0.71%) across three decades that did not influence the overall frequency of idiopathic disease. PCR of aqueous fluid for diagnosis of herpetic eye disease was first described in 1991.[32] Since

that time, the test has become readily available at medical institutions. At our institution, the diagnosis of herpetic CAU is typically based on clinical findings such as elevated intraocular pressure and atrophy of the posterior pigment epithelium of the iris. In patients with these clinical findings, PCR of aqueous fluid is not typically performed. Therefore, the frequency of herpetic disease may be under-diagnosed, particularly in cases with an atypical presentation.

Three of the less common etiologies of CAU showed an increase in frequency of diagnosis over the course of this study. IBD-related uveitis showed an increase in relative frequency.   The recognition of the strong association between a personal family history of IBD and uveitis has likely contributed to this increase.[23]

Multiple sclerosis (MS) showed an increase of approximately 1% in the latest decade (1995-2004) when compared to the earliest decade (1975-1984). The diagnosis of MS has increased in recent years, perhaps related to the increased use of neuroimaging and/or the increased lifespan of patients diagnosed with MS.[33]

HLA-B27 associated uveitis showed an increase in frequency of diagnosis over time. This is classically described as an acute, recurrent anterior uveitis, although some patients develop chronic disease. The increased use of HLA-B27 testing in the mid- to late- 1970s and recent switch from serological testing to polymerase chain reaction (PCR) may have contributed to the increase in frequency of this diagnosis.[34] Most patients with chronic disease are not tested for HLA-B27 in our clinic, which may have resulted in an underestimation of the frequency of diagnosis of this condition.

This study has many limitations, including its retrospective nature and the lack of demographic data on all of the patients. As was shown for the FHI cohort of patients, the change in frequency of diagnosis cannot always be fit by linear regression, which makes the comparison between the diagnoses more difficult. It is also possible that the measured trends were influenced by referral patterns, as was hypothesized for JIA. As well, this study is based on a tertiary referral practice, and may not be applicable to the uveitis population at large. Despite these limitations, we believe that this analysis of almost 2,000 patients   seen over a span of more than three decades provides valuable information regarding patterns of chronic anterior uveitis over time.

In this study, we set out to determine if recent advances in the diagnosis of chronic anterior uveitis and newly described etiologies have translated into a decreased frequency of idiopathic disease over time, and we documented a small but statistically significant decrease. Fluctuations in referral patterns may have influenced this decrease, as have increases in the frequency of CAU associated with the HLA-B27 allele, personal and/or family history of IBD, and diagnosis of multiple sclerosis. In spite of all of our advances over the last 35 years, however, more than one-third of all CAU has remained idiopathic. We clearly still have a long way to go in the understanding of the etiopathogenesis of chronic anterior uveitis.

Acknowledgements:

References:

1. Rodriguez A, Calonge M, Pedroza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. *Arch Ophthalmol* 1996;114(5):593-599.

2. Paivonsalo-Hietanen T, Tuominen J, Vaahtoranta-Lehtonen H, et al. Incidence and prevalence of different uveitis entities in Finland. *Acta Ophthalmol Scand* 1997;75(1):76-81.

3. Khairallah M, Yahia SB, Ladjimi A, et al. Pattern of uveitis referral centre in Tunisia, North Africa. *Eye* 2007;21(1):33-39.

4. Soheilian M, Heidari K, Yazdani S, et al. Patterns of uveitis in a tertiary eye center in Iran. *Ocul Immunol Inflamm* 2004;12(4):297-310.

5. McCannel CA, Holland GN, Helm CJ, et al. Causes of uveitis in the general practice of ophthalmology. UCLA Community-based Uveitis Study Group. *Am J Ophthalmol* 1996;121(1):35-46.

6. Mercanti A, Parolini B, Bonora A, et al. Epidemiology of endogenous uveitis in north-eastern Italy. Analysis of 655 new cases. *Acta Ophthalmol Scand* 2001;79(1):64-68.

7. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California: The Northern California epidemiology of uveitis study. *Ophthalmology* 2004;111(3):491-500.

8. Sengun A, Karadag R, Karakurt A, et al. Causes of uveitis in a referral hospital in Ankara, Turkey. *Ocul Immunol Inflamm* 2005;13(1):45-50.

9. Smit R, Baarsma GS, de Vries J. Classification of 750 consecutive uveitis patients in the Rotterdam Eye Hospital. *Int Ophthalmol* 1993;17(2):71-75.

10. Rothova A, Buitenhuis HJ, Meenken C, et al. Uveitis and systemic disease. *Br J Ophthalmol* 1992; 76(3)137-141.

11. Palmares J, Coutinho MF, Castro-Correia J. Uveitis in northern Portugal. *Curr Eye Res* 1990;9 Suppl:31-34.

12. Suhler EB, Lloyd MJ, Choi D, et al. Incidence and prevalence of uveitis in Veterans affairs medical centers of the Pacific Northwest. *Am J Ophthalmol* 2008;146(6):890-96.

13. Paivonsalo-Hietanen T, Vaahtoranta-Lehtonen H, Tuominen J, et al. Uveitis survey at the University Eye Clinic in Turku. *Acta Ophthalmol* 1994;72(4):505-512.

14. Biswas J, Narain S, Das D, et al. Pattern of uveitis in a referral uveitis clinic in India. *Int Ophthalmol* 1996;20(4):223-238.

15. Islam SM, Tabbara KF. Causes of uveitis at The Eye Center in Saudi Arabia: a retrospective review. *Ophthalmic Epidemiol* 2002;9(4):239-249.

16. Weinberg RS, Tessler HH. Serum lysozyme in sarcoid uveitis. Am J Ophthalmol 1976;82:105-108.

17. Weinreb RS, Tessler HH. Laboratory diagnosis of ophthalmic sarcoidosis. *Surv Ophthalmol* 1984;28(6):653-664.

18. Kaiser PK, Lowder CY, Sullivan P, et al. Chest computerized tomography in the evaluation of uveitis in elderly women. *Am J Ophthalmol* 2002;133(4):499-505.

19. Vanhaesebrouck P, Carton D, De Bel C, et al. Acute tubulo-interstitial nephritis and uveitis syndrome (TINU syndrome). *Nephron* 1985;40(4):418-422.

20. Birnbaum AD, Tessler HH, Schultz KL, et al. Epidemiologic relationship between Fuchs heterochromic iridocyclitis and the United States rubella vaccination program. *Am J Ophthalmol* 2007;144(3):424-428.

21. Quentin CD, Reiber H. Fuchs heterochromic cyclitis: rubella virus antibodies and genome in aqueous humor. *Am J Ophthalmol* 2004;138(1):46-54.

22. de Groot-Mijnes JD, de Visser L, Rothova A, et al. Rubella virus is associated with fuchs heterochromic iridocyclitis. *Am J Ophthalmol* 2006;141(2):212-214.

23. Lin P, Tessler HH, Goldstein DA. Family history of inflammatory bowel disease in patients with idiopathic ocular inflammation. *Am J Ophthalmol* 2006;141(6):1097-104.

24 Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47(2):155-170.

25. Bloch-Michel E, Nussenblatt RB. International Uveitis study Group recommendations for the evaluation of intraocular inflammatory disease. Am J Ophthalmol. 1987;103(2):234-235.26. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140(3):509-516.

27. Pivetti-Pezzi P, Accorinti M, La Cava M, et al. Endogenous Uveitis: An analysis of 1417 Cases. *Opthalmologica* 1996;210(4):234-238.

28. Weinreb RN, O'Donnell JJ, Sandman R, et al. Angiotensin-converting enzyme in sarcoid uveitis. *Invest Ophthalmol Vis Sci* 1979;18(12):1285-1287.

29. Franceschetti A. Heterochromic cyclitis: Fuchs' syndrome *Am J Ophthalmol* 1955;39(4, Part 2):50-58.

30. Kimura SJ, Hogan MJ, Thygeson P. Fuchs' syndrome of heterochromic cyclitis. *AMA Arch Ophthalmol* 1955;54(2):179-186.

31. Kaipiainen-Seppanen O, Savolainen A. Changes in the incidence of juvenile rheumatoid arthritis in Finland. Rheumatology 2001;40(8): 928-932.

32. Fox GM, Crouse CA, Chuang EL, et al. Detection of herpesvirus DNA in vitreous and aqueous specimens by the polymerase chain reaction. *Arch Ophthalmol* 1991:109(2):266-271.

33. Ragonese P, Aridon P, Salemi G, D'Amelio M, Savettieri G. Mortality in multiple sclerosis: a review. *Eur J Neurol* 2008;15(2):123-127.

34. Kirveskari J, Kellner H, Wuorela M, et al. False-negative serological HLA-B27 typing results may be due to altered antigenic epitopes and can be detected by polymerase chain reaction. *Br J Rheumatol* 1997;36(2):185-189.
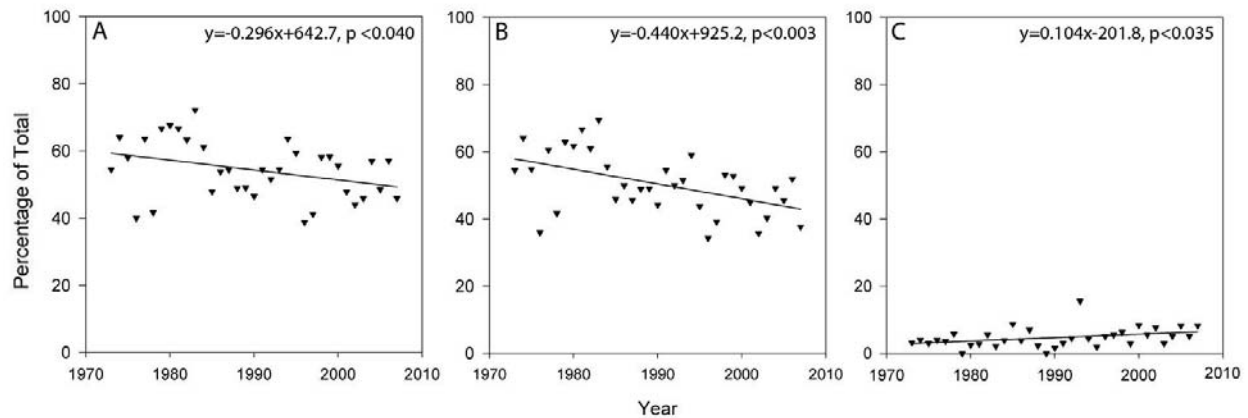
Figures

Figure 1. Change in frequency of diagnosis of idiopathic chronic anterior uveitis over time. A. A statistically significant decrease in relative frequency of diagnosis of idiopathic disease was noted in patients evaluated between 1973 and 2007. B. The decrease in relative frequency of idiopathic disease in adult patients was of greater magnitude than that measured in patients of all ages. C. A significant increase in frequency of diagnosis of idiopathic disease was measured over time in children (16 years or younger) .
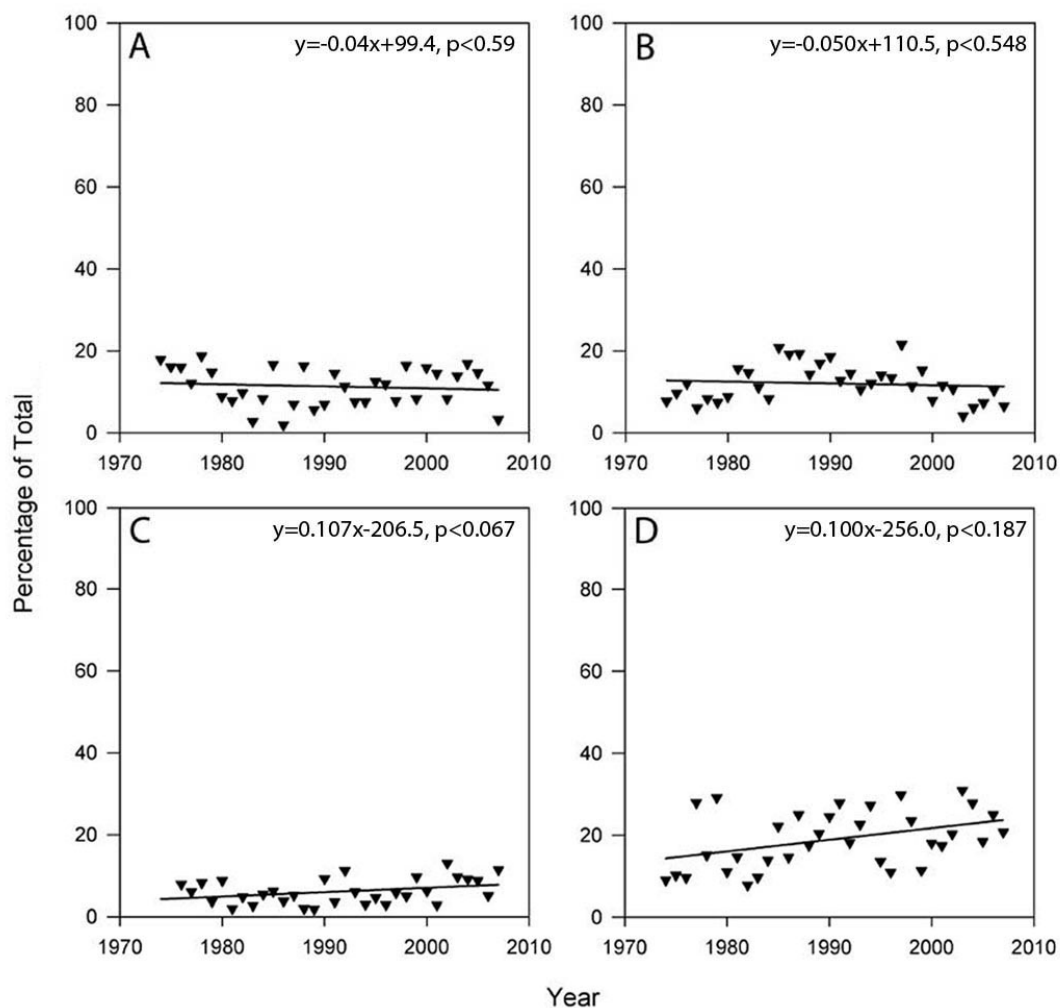
Figure 2. Change in frequency of diagnosis of FHI, sarcoidosis, JIA and other diagnosis over time. The diagnosis of FHI (Box A), sarcoidosis (Box B), and JIA (Box C) did not change significantly over time. D. The combination of diagnoses making up less than 5% of chronic anterior uveitis over time were combined, and a significant change in frequency of diagnosis was not measured.