

Chronic Infantile Neurological Cutaneous and Articular/Neonatal Onset Multisystem Inflammatory Disease Syndrome

Ocular Manifestations in a Recently Recognized Chronic Inflammatory Disease of Childhood

Hélène Dollfus, MD; Renate Häfner, MD; Hans Martin Hofmann, MD; Ricardo A. G. Russo, MD; Leandro Denda, MD; Luis Diaz Gonzales, MD; Carmen DeCunto, MD; Jorge Premoli, MD; José Melo-Gomez, MD; José Pedro Jorge, MD; Richard Vesely, MD; Michal Stubna, MD; Jean-Louis Dufier, MD; Anne-Marie Prieur, MD; and the International Chronic Infantile Neurological Cutaneous and Articular/Neonatal Onset Multisystem Inflammatory Disease (CINCA/NOMID) Ocular Study Group

Objective: To report on the ocular manifestations of the Chronic Infantile Neurological Cutaneous and Articular/Neonatal Onset Multisystem Inflammatory Disease (CINCA/NOMID) syndrome, a rare, recently identified, pediatric multisystem inflammatory disease with chronic cutaneous, neurological, and articular manifestations.

Design: Descriptive case-report study.

Setting: International collaborative study based on a questionnaire.

Results: We included 31 patients. The mean age at onset of eye manifestations was 4.5 years. Optic disc changes were the most common feature, occurring in 26 patients (83%), including optic disc edema, pseudopapill-

edema, and optic atrophy. Anterior segment manifestations varying from mild to severe were seen in 13 patients (42%); chronic anterior uveitis, in 17 patients (55%). Moderate to severe visual acuity loss in at least 1 eye was seen in 8 patients (26%) as a consequence of the disease. Posterior synechia, glaucoma, and white iritis were not observed in any patient.

Conclusion: Ocular manifestations with potentially sight-threatening complications occur commonly in the CINCA/NOMID syndrome. The distinctive nature of these complications may assist the ophthalmologist in recognizing this rare disorder and distinguishing it from juvenile rheumatoid arthritis.

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The affiliations of the authors appear in the acknowledgment section at the end of the article. A complete list of the members of the International CINCA/NOMID Ocular Study Group is provided in the box on page 1391.

THE CHRONIC Infantile Neurological Cutaneous and Articular/Neonatal Onset Multisystem Inflammatory Disease (CINCA/NOMID) syndrome is a rare inflammatory pediatric disease identified as a new clinical entity by Prieur et al¹ in 1987. About 60 cases have been reported in the literature.¹⁻⁹ However, it is possible that patients with mild or moderate forms have not been identified because the clinical presentation and course vary among individual patients.

This syndrome is characterized by a skin rash, joint manifestations, and involvement of the central nervous system, including the sensory organs. The symptoms are clearly distinct from known chronic inflammatory rheumatic disorder in children.^{10,11} The first symptoms occur at birth or in the first 6 months of life. The skin rash, a chronic nonpruritic urticaria varying during the day, is usually

the first symptom (**Figure 1**). Articular manifestations involving the knees (**Figure 1**), ankles, feet, elbows, wrists, and hands range from joint swelling occurring during flare-ups to severe bone changes with unique radiological features¹² (**Figure 2**). Neurological abnormalities are characterized by chronic meningitis and secondary cerebral atrophy. Mental retardation has been noted in some patients. Sensory organ involvement has been observed, including ocular manifestations and progressive sensorineural hearing loss leading to deafness in 22% of patients. Hoarseness may develop gradually. Morphologic features include short stature, macrocephaly, saddle nose, and short, thick extremities with clubbing of fingers.^{1,13,14}

The course of the disorder is one of a chronic relapsing inflammatory disease with fever, splenomegaly, and lymphadenopathy. Results of laboratory studies show non-specific features of inflammation. A genetic predisposition may exist, but a specific

PATIENTS AND METHODS

CASE DEFINITION

The criteria used to diagnose the CINCA/NOMID syndrome are the presence of an evanescent rash, nonpruritic and varying during the day, most often of neonatal onset, with joint involvement (mild or severe arthropathy) and/or chronic meningitis.¹¹ Neurological clinical manifestations include meningeal irritation (eg, headaches, seizures, spasticity of legs), cerebral atrophy, subnormal intelligence, sensorial involvement (eg, deafness, ocular manifestations), and hoarseness. This diagnosis is established by pediatric rheumatologists.

QUESTIONNAIRE

A questionnaire, conceived to investigate the ocular status of patients affected by the CINCA/NOMID syndrome, was sent to pediatric rheumatologists worldwide. The questionnaire had to be answered from July 1, 1996, to January 31, 1997, with the collaboration of the patient's ophthalmologist.

DEMOGRAPHIC EVALUATION

Demographic data and medical history were available for each patient on an anonymous basis. The date of birth as well as the date and cause of death, when applicable, were reviewed. The ages at the first CINCA/NOMID symptom, at diagnosis, and at first ocular sign were recorded.

GENERAL EVALUATION

The clinical manifestation needed for inclusion in the study was the association of neurological, cutaneous, and articular symptoms, as summarized above. The following general data concerning the disease were recorded: presence or absence of fever, skin manifestations (mild or severe), arthropathy (transient flares without radiographic changes or severe arthropathy with radiographic changes), central nervous system involvement (cerebral spinal fluid cell count and differential), deafness, and hoarseness. Other cases of CINCA/NOMID syndrome in the patient's family were recorded.

EVALUATION OF OCULAR MANIFESTATIONS

Evaluation of Visual Function

Visual acuity in each eye was recorded on the first and the last ocular examination. As different visual acuity charts (6-m and 20-ft Snellen and decimal) were used for the recordings, the visual acuity measurements were converted to the Snellen 20-ft notation.^{15,16} The visual status of the patient was classified into one of the following categories^{17,18}: binocular severe loss (both eyes, <20/400), binocular moderate loss (1 eye, 20/400-20/80; other eye, same or worse), monocular severe loss (1 eye, <20/400; other eye, >20/80), monocular moderate loss (1 eye, 20/400-20/80; other eye, >20/80), and mild loss or adequate visual acuity (both eyes, >20/80).

Anterior Segment Evaluation

The anterior segment was evaluated by asking the following questions: presence or absence of dry eye (Schirmer test, tear breakup, and specific treatment) and presence or absence of conjunctival or scleral lesions (chronic conjunctivitis, episcleritis, chronic perilimbal redness, scleritis, scleral nodules, and other lesions). We attempted to determine whether episodes of conjunctival hyperemia coincided with systemic flare-ups.

The presence or absence of band keratopathy, epithelial or endothelial abnormality, corneal neovascularization, and infiltrative stromal keratopathy were determined. Medical and/or surgical treatments for these conditions were documented.

The presence or absence of iris nodules, anterior or posterior synechia, and anterior uveitis was recorded. The severity and periodicity of the uveitic episodes were graded according to the lowest, highest, and current number of cells and the degree of flare in the anterior chamber. The frequency of the ocular flare-ups and concomitant relapse of other systemic features of the syndrome were documented. The presence of cataract, including the date of diagnosis, type, and treatment, was recorded. Intraocular pressure for each eye, with the lowest and highest recorded measurements and measurements at last examination, was documented. The cup-disc ratio, visual field results, if available, and nature of antiglaucomatous treatment were also recorded.

Posterior Segment Evaluation

The evaluation of the posterior segment included the presence or absence of vitritis (specifying the number of cells with the mildest and the most severe, and current degree) and the presence or absence of small gelatinous vitreous exudates (snowballs), peripheral vasculitis, and snowbanking in the inferior pars plana suggestive of pars planitis.

The choroid and the retina were investigated by the following questions: presence or absence of retinochoroidal infiltrates, vasculitis (diffuse or focal), cotton-wool spots, macular edema, and retinal detachment (rhegmatogenous or nonrhegmatogenous).

The optic discs were examined for signs of papilledema, pseudopapilledema, and optic atrophy. Documentation using fundus photography, fluorescein angiography, visual field results, and any other ocular investigations was obtained when possible.

We designated optic disc edema (avoiding confusion with papilledema exclusively due to elevated intracranial pressure¹⁹) as an elevated, swollen optic disc with evidence of capillary dilation on results of fundus examination and fluorescein angiography, microaneurysm formation, early dye leakage, and residual fluorescence beyond the disc margins in the late phase.^{19,20} We referred to pseudopapilledema when the optic disc appeared swollen on results of long-term repeated examinations, but disclosed discrete capillary and vascular changes with very faint or absent early leakage and no residual late-phase leakage on fluorescein angiographic findings. The stability of the optic disc elevation over time was one of the criteria for diagnosis of pseudopapilledema. No patient with pseudopapilledema was found to have drusen to date.

in utero infection or an environmental cause cannot be excluded. The cause, pathophysiology, and treatment of the CINCA/NOMID syndrome remain unknown. The severity of the disease is variable, and death may occur in young

adulthood in 20% of the patients¹ because of infection, secondary amyloidosis, or cachexia.

The differential diagnosis includes systemic juvenile rheumatoid arthritis (JRA), hyperimmunoglobulin



Figure 1. Cutaneous rash and severe arthropathy in a 6-year-old child with the Chronic Infantile Neurological Cutaneous and Articular/Neonatal Onset Multisystem Inflammatory Disease syndrome.

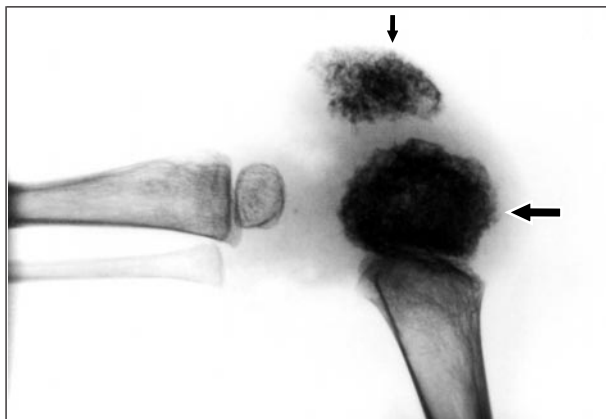


Figure 2. X-ray of the knee of the patient in Figure 1, showing a grossly enlarged epiphysis of the femoral extremity and patella hypertrophy with punctate increased density.

linemia D syndrome, Sweet disease, histiocytosis, mastocytosis, late-onset neonatal rubella syndrome, a metabolic storage disease, and Muckle-Wells syndrome.

Ocular manifestations appear to be common in this disease, with potential sight-threatening complications. To characterize better the ocular manifestations and the visual outcome of patients with the CINCA/NOMID syndrome, an international collaborative study was undertaken. We present herein the data gathered by this study concerning the main ocular manifestations of this disease.

RESULTS

DEMOGRAPHIC AND GENERAL DATA

Thirty-one patients with the CINCA/NOMID syndrome were included in this study. The geographic origin of these were as follows: 5 patients from Argentina; 2 from Canada, 1 from Finland, 11 from France, 1 from Great Britain, 3 from Germany, 1 from Holland, 1 from Italy, 2 from Portugal, 2 from the United States, and 2 from Slovakia. Nine patients (29%) were male; 22 (71%), female (male:female sex ratio, 1:3.5). At the time of the study, 2 pa-

Table 1. Anterior Segment Abnormalities

Abnormality	No. (%) of Patients With Abnormality	Comments
Dry eye	4 (13)	3 Mild (75%); 1 severe (25%)
Episodic redness	15 (48)	...
Chronic conjunctivitis	5 (16)	...
Perilimbal redness	10 (32)	...
Corneal involvement	13 (42)	7 Mild (54%); 6 severe (46%)
Band keratopathy	8 (26)	...
Stromal infiltration	7 (23)	...
Corneal neovascularization	3 (10)	...
Cataract	5 (16)	Mild to moderate, nonsurgical
Glaucoma	0 (0)	...
Anterior uveitis	16 (52)	Mild to moderate for 9 (56%); severe for 7 (44%)
Iris	...	No posterior synechia

tients were younger than 6 years, 21 were aged 6 through 18 years, and 8 were adults. They all fulfilled the clinical criteria for CINCA/NOMID syndrome. Systemic manifestations for the patients of the study are summarized in the following tabulation:

Systemic Feature	No. (%) of Patients
Rash	28 (90)
Fever	27 (87)
Arthropathy	27 (87)
Chronic meningitis	23 (74)
Deafness	20 (65)
Hoarseness	3 (10)

The duration of clinical follow-up ranged from 2 to 32 years, with a mean of 11.5 years.

In 27 patients, the first symptoms occurred in the first month of life; in 3, before 6 months of age. Despite this early clinical presentation, the mean age of diagnosis for the CINCA/NOMID syndrome was 6.5 years. Six patients received a diagnosis before 1 year of age; 17, at ages 1 through 10 years; and 5, at older than 10 years. The age at diagnosis was unknown in 2 patients. The youngest patient was aged 2 months at the time of diagnosis; the oldest, aged 27 years.

At the time of the study, 4 patients (3 male and 1 female) were dead. Two of these died of chronic renal failure due to secondary amyloidosis; 1 of pneumonia; and 1 of pulmonary and heart failure.

OCULAR MANIFESTATIONS DATA

The age at the first ocular sign was available for 25 patients. The mean age at the first ocular sign was 4.5 years (range, 1 month to 9 years). The following first ocular signs were known for 22 patients: red eyes (7 patients), decreased vision (7 patients), strabismus (4 patients), nystagmus (2 patients), and photophobia (2 patients). In 5 patients, the first ocular manifestation was discovered on results of fundus examination when an abnormal optic disc was seen. Symptoms at initial examination included blurred vision in 7 patients and photophobia in 3.

Visual Acuity and Visual Function

Visual acuity findings were available in 30 patients. Nineteen had adequate visual acuity or mild visual loss; 3, monocular moderate visual loss. Eight patients (27%) had monocular or binocular, moderate or severe visual loss. Visual loss in 7 patients was classified as bilateral moderate and in 1 patient as monocular severe (no patient received a classification of binocular severe visual loss). All 8 patients had signs of optic nerve involvement (2 with optic disc edema, 6 with optic atrophy), and 6 also had corneal involvement (4 with band keratopathy and 2 with infiltrative keratopathy). Mental impairment, when present, did not seem to affect the assessment of visual acuity.

Anterior Segment

Data concerning the anterior segment were available for all 31 patients (**Table 1**). Four patients (13%) were first seen with a dry eye; in 1 patient it was severe. Chronic eye

redness was noticed in 13 patients (42%). Eight patients were recorded as having chronic perilimbal injection; 3, chronic conjunctivitis; and 2, both. For 2 patients, the red eye occurred at the same time as the skin rash.

Of thirteen patients (42%) with progressive corneal abnormalities, 5 also had chronic eye redness. Seven patients were first seen with stromal opacification, band keratopathy developed in 8, and 3 had corneal neovascularization. Six patients were classified as having severe corneal involvement, 1 of whom eventually underwent bilateral penetrating keratoplasty. This patient was first seen with corneal abnormalities that extended slowly from the periphery to the center of the cornea; results of histopathologic examination showed linear calcification in the medial stroma. Between the medial and posterior stroma, there was an interstitial keratitis with histiocytes and lymphocytes and intrastromal neovascularization (Marc Puttermann, MD, Paris, France, oral communication, May 1996). **Figure 3** shows another patient with identical slowly progressive peripheral corneal abnormalities.

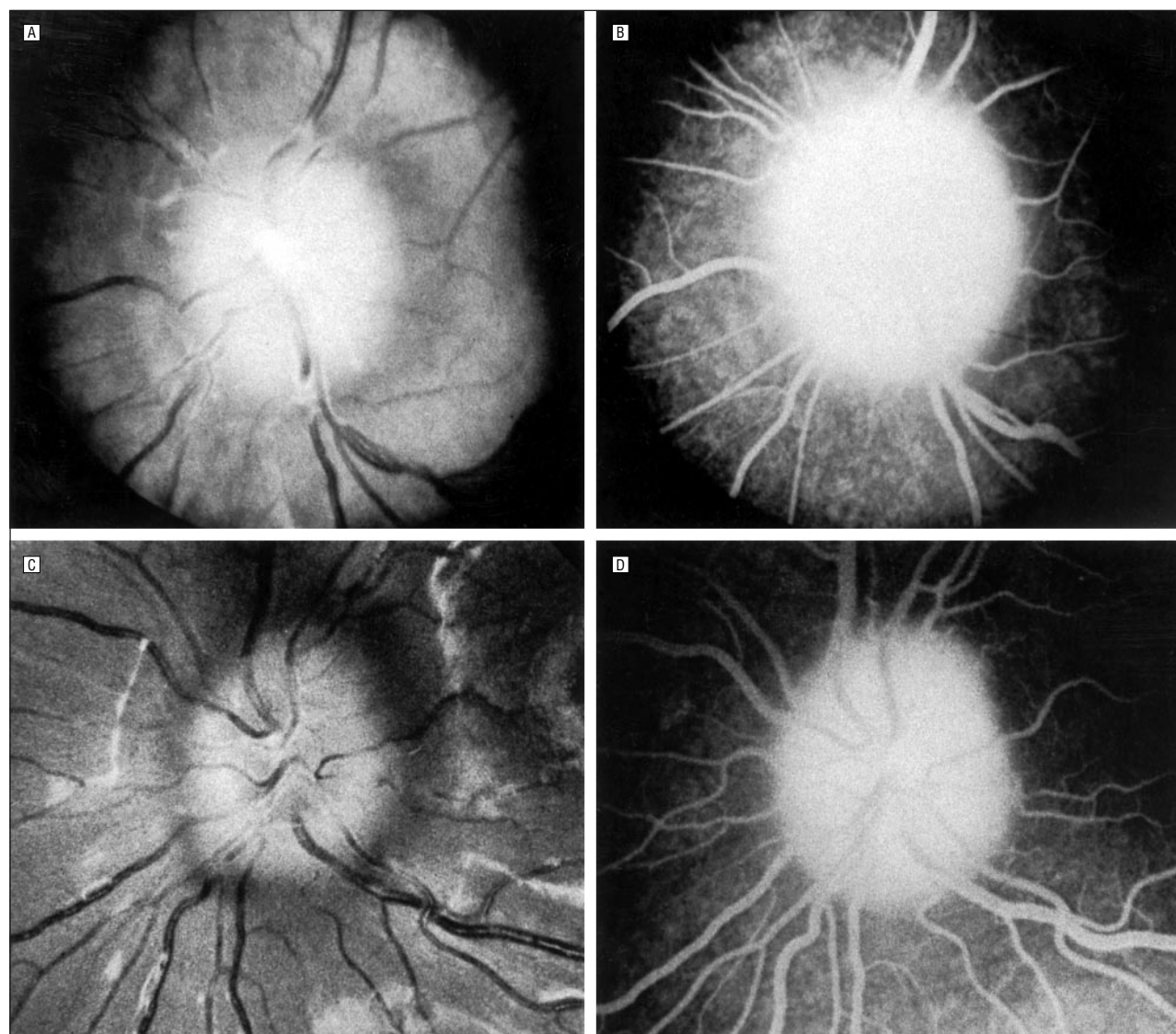


Figure 3. Fundus photograph (A) and late stage of fluorescein angiogram (B) of a patient with the Chronic Infantile Neurological Cutaneous and Articular/Neonatal Onset Multisystem Inflammatory Disease (CINCA/NOMID) syndrome showing optic disc edema. Fundus photograph (C) and late stage of fluorescein angiogram (D) of a patient with the CINCA/NOMID syndrome showing pseudopapilledema.

Table 2. Posterior Segment Abnormalities

Abnormality	No. (%) of Patients With Abnormality	Comments
Vitritis	4 (13)	2 Moderate; 2 severe
Pars planitis	0 (0)	...
Vasculitis	3 (10)	...
Focal chorioretinitis	1 (3)	...
Macular edema	4 (13)	All mild
Optic disc abnormality	26 (84)	...
Papilledema	13 (42)	...
Pseudopapilledema	7 (23)	...
Optic atrophy	9 (29)	...

Of 16 patients with anterior uveitis, 9 had mild iritis and only 1 patient had keratic precipitates. The estimated frequency of iridocyclitis ranged from 1 to several episodes annually. Eight patients were treated with topical steroids, 4 with improvement and 4 with minimal improvement.

No iris involvement, including anterior and posterior synechiae, was noticed in any of the patients.

Five patients had mild cataracts, none of which has required surgical intervention to date.

None of the patients involved in this study had documented glaucoma or elevated intraocular pressure.

Posterior Segment

Signs of posterior inflammation were found for 6 patients (19%). Four patients (13%) had vitritis, moderate in 2 (≥ 1 cells) and more severe in 2 (≥ 2 cells). No patients had pars planitis. Three patients had retinal vasculitis and 1 patient had a focal chorioretinitis. Moderate cystoid macular edema was present in 4 patients (**Table 2**). One patient had an epiretinal membrane.

Optic Disc

Twenty-six patients (84%) had optic disc abnormalities. Twenty patients (65%) had optic disc edema (**Figure 4**). Fluorescein angiogram confirmed optic disc edema in 13 patients (42%). Seven patients (23%) had pseudopapilledema. Seventeen of the 20 patients with optic disc edema had chronic meningitis. Anterior uveitis and posterior uveitis was present in 7 and 2 patients with optic disc edema, respectively. Nine patients (29%) had moderate to severe diffuse optic atrophy. The appearance of the discs was symmetrical for both eyes.

FAMILIAL HISTORY

A familial occurrence of this syndrome was observed in 2 French families (a father and daughter in 1 family and a mother and a daughter in another), suggesting a possible genetic predisposition for the disease. Their ocular involvement was not different from that of the other patients.

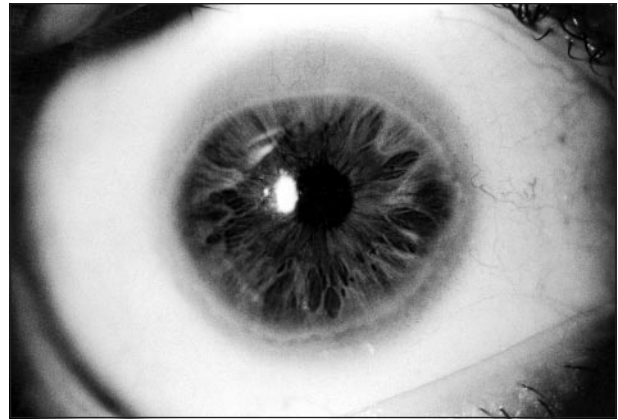


Figure 4. Anterior segment photograph of a 43-year-old patient with the Chronic Infantile Neurological Cutaneous and Articular/Neonatal Onset Multisystem Inflammatory Disease syndrome showing peripheral corneal abnormalities.

COMMENT

The CINCA/NOMID syndrome is a rare chronic pediatric inflammatory disease consisting of chronic arthropathy, skin rash, chronic meningitis, and sensory organ involvement. Ocular manifestations have been documented,^{1,3,4,7,9,21-23} but to our knowledge, their frequency and severity have not been studied systematically. The cause of this disorder remains unknown.

One of the difficulties in studying such a rare syndrome is in collecting homogeneous clinical data to estimate the frequency and severity of each ocular manifestation and their implication for vision. This worldwide descriptive case study seemed to us the only feasible and possibly reliable way to gather consistent data while remaining conscious of the multiple observers involved.

During the time of observation, 26% of the patients were defined as having monocular moderate visual loss or worse. These results probably underestimate the ocular morbidity of the CINCA/NOMID syndrome because of the lack of long-term systematic review in many patients. Nevertheless, it appears that some patients have severe systemic and ocular manifestations, whereas others have milder disease. The ocular severity does not always correlate with the systemic severity, as for some patients the ocular involvement was minimal in the presence of severe systemic features.

Chronic perilimbal injection as well as chronic conjunctivitis were frequently present. This sign distinguishes the iridocyclitis in CINCA/NOMID from the classic white eye found among the ocular complications of JRA.²⁴

In most patients, anterior ocular inflammation was a mild to moderate nongranulomatous anterior uveitis, although some patients had severe anterior uveitis. Unlike children with JRA, posterior synechiae did not develop in any patient with anterior uveitis. Similarly, glaucoma or severe cataract requiring surgery did not develop in any patients. Although the CINCA/NOMID may be confused initially with systemic JRA, the short duration of bouts of fever, the characteristics of the rash, the presence of joint disease, and the existence of central nervous system manifestations usually differentiate between the two. Further-

Buenos Aires, Argentina: Ricardo A. G. Russo, MD (PR), Leandro Denda, MD (OPH), Luis Diaz Gonzales, MD (OPH), Hospital de Pediatria J P Garrahan; Carmen DeCunto, MD (PR), Jorge Premoli, MD (OPH), Hospital Italiano. **Hamilton, Ontario:** Peter B. Dent, MD, FRCP (PR), Children's Hospital; Patricia T. Harvey, MD (OPH), McMaster University Medical Center. **Nottingham, England:** Helen Venning, FRCP, FRCPCH (PR), Roger Allen, MD (DER), Richard Downes, FRCS, FRCOphth (OPH), Queens Medical Center. **London, England:** Patricia Woo, MD, PhD (PR), Windeyer Institute, University College of London; Elisabeth Graham, MD (OPH), St Thomas Hospital. **Helsinki, Finland:** Pirkko Pelkonen, MD, PhD (PR), Marjatta Lappi, MD (OPH), Helsinki University Central Hospital. **Paris, France:** Anne-Marie Prieur, MD (PR), Hélène Dollfus, MD (OPH), Jean-Louis Dufier, MD (OPH), Hôpital Necker-Enfants Malades. **Rennes, France:** Jacqueline Chevrant-Breton, MD (DER), Martine Urvoy, MD (OPH), Centre Hospitalier Universitaire, Pontchaillou. **Brest, France:** Jean-Marie Lefur, MD (PR), Anne Robinet, MD (OPH), Hôpital Morvan. **Garmisch-Partenkirchen, Germany:** Renate Häfner, MD (PR), Rheumakinderklinik; Hans Martin Hofmann, MD (OPH), Sonnenbergstrasse. **Heidelberg, Germany:** Christiane C. G. Sakmann, MD (OPH), Wieckenstrasse. **Leiden, Holland:** Rebecca ten Cate, MD, PhD (PR), Robert J. W. De Keizer, MD (OPH), Leiden University Medical Center. **Trieste, Italy:** Loredana Lepore, MD (PR), Agatino Vinciguerra, MD (OPH), Ospedale Infantile. **Lisboa, Portugal:** José A. Melo-Gomes, MD (PR), Instituto Portugues de Reumatologia; José Pedro Jorge, MD (OPH), Hospital Militar Principal. **Kosice, Slovakia:** Richard Vesely, MD (PR), Frantisek Vesely, MD (OPH), Stubna Michal, MD (OPH), Faculty Hospital. **Indianapolis, Ind:** Suzanne L. Bowyer, MD (PR), Indiana University School of Medicine, Hospital for Children; Forrest D. Ellis, MD (OPH), Midwest Eye Institute. **Philadelphia, Pa:** Lois Martyn, MD (PR), Temple University Children's Medical Center; Donald Goldsmith, MD (PR), St Christopher Hospital for Children. **Louisville, Ky:** Kenneth Schickler, MD (PR), University of Louisville School of Medicine.

*PR indicates pediatric rheumatologist; OPH, ophthalmologist; and DER, dermatologist.

more, polyarticular JRA, accounting for 20% of all patients with JRA, is rarely associated with uveitis. The anterior uveitis features in the CINCA/NOMID syndrome differ dramatically from eye manifestations in oligoarticular JRA, in which anterior uveitis is complicated by posterior synechiae, glaucoma, and cataracts.

In the CINCA/NOMID syndrome, posterior inflammation seems to occur less frequently than anterior segment inflammation, but in some patients, vitritis and vasculitis may occur.

Band keratopathy, which is due to accumulation of hydroxyapatite in the Bowman membrane, is a common complication of chronic inflammation, especially in JRA. Interstitial keratitis with stromal infiltration, as confirmed by the pathological report after a bilateral penetrating keratoplasty in 1 patient of this study, may be a specific finding of the CINCA/NOMID syndrome compared with JRA. The corneal opacification progressed slowly from the periphery to the center of the cornea, with peripheral infiltrate seen on the slitlamp biomicroscopic findings. This finding was bilateral and had no infectious origin.

An abnormal optic disc appearance was the most common ocular manifestation of the CINCA/NOMID syndrome. Optic disc elevation and/or atrophy was recorded in 83% of the patients. The chronic meningo-encephalitis associated with the CINCA/NOMID syndrome may explain the presence of optic disc swelling and the eventual development of atrophy. Meningitis may cause inflammatory or infectious optic disc swelling as a result of increased intracranial pressure or optic disc perineuritis.²⁵ Cerebrospinal fluid was under normal pressure in all patients except one. Results of cerebrospinal fluid analysis in most patients showed increased numbers of white blood cells but without evidence of infection. A few patients with optic disc swelling also had anterior or posterior uveitis that may have contributed to the optic disc swelling. Optic nerve involvement

Table 3. Comparison of Main Ocular Manifestations of JRA vs CINCA/NOMID*

Ocular Manifestation	JRA	CINCA/NOMID
Red eye	–	+
Band keratopathy	+	+
Stromal keratopathy	–	+
Anterior uveitis	++	+
Secondary cataract	+	–
Secondary glaucoma	+	–
Posterior synechiae	+	–
Optic nerve involvement	+/-	+ to ++
Papilledema	+/-	++
Optic atrophy	–	+

*JRA indicates juvenile rheumatoid arthritis; CINCA/NOMID, chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease; minus sign, not found; plus/minus signs, occasional feature; plus sign, common feature; and double plus sign, very frequent feature.

appears to be more common in the CINCA/NOMID syndrome than in JRA.

Inherent limitations of this multicenter study have to be underlined, such as the retrospective nature of the study and the possible tendency to select out severe forms of the disease. Moreover, severe signs may have caused mild ones to be overlooked. In addition, visual loss in a patient may be difficult to assign, because when multiple contributory ocular signs coexist, some may obscure others.

Familiarity with the unique profile of ocular complications in the CINCA/NOMID syndrome will assist the ophthalmologist in diagnosing this rare disorder and distinguishing it from JRA (**Table 3**). Once the diagnosis of CINCA/NOMID syndrome is established, the ophthalmologist should remain an integral part of the management team, since vision-threatening complications may develop. Further study and follow-up of patients with the CINCA/NOMID syndrome will be necessary to eluci-

date the long-term visual morbidity and optimal treatment strategies for this rare disorder.

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From the Department of Ophthalmology (Drs Dollfus and Dufier) and Unité d'Immuno-Hématologie Pédiatrique, Hôpital Necker-Enfants Malades, Paris, France; Rheumakinderklinik (Dr Häfner) and Sonnenbergstrasse (Dr Hofmann), Garmisch-Partenkirchen, Germany; Departments of Pediatrics (Dr Russo) and Ophthalmology (Drs Denda and Diaz Gonzales), Hospital de Pediatría J P Garrahan, and Departments of Pediatrics (Dr DeCunto) and Ophthalmology (Dr Premoli), Hospital Italiano, Buenos Aires, Argentina; Department of Pediatrics (Dr Melo-Gomes) and Ophthalmology (Dr Jorge), Hospital Militar Principal, Lisboa, Portugal; and the Departments of Pediatrics (Dr Vesely) and Ophthalmology (Dr Stubna), Faculty Hospital, Kosice, Slovakia.

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Reprints: Hélène Dollfus, MD, Service de Génétique Médicale et Service d'Ophtalmologie, Hôpitaux Universitaires de Strasbourg, 67089 Strasbourg, France, and Anne-Marie Prieur, MD, UIH, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, Université Paris V, 75015 Paris, France.

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