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ORIGINAL PAPER

Indocyanine green angiography in Vogt–Koyanagi–Harada disease: angiographic signs and utility in patient follow-up

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Abstract *Purpose* Firstly, to give a review of characteristic indocyanine green angiographic (ICGA) signs in Vogt–Koyanagi–Harada (VKH) disease and, secondly, to determine the utility of ICG angiography in the assessment and follow-up of choroidal inflammatory activity during initial high-dose inflammation suppressive therapy and during the tapering of therapy.

Methods We have first reviewed characteristic ICGA signs in VKH. This is followed by a study of four patients with an acute initial VKH uveitis episode who received regular initial and follow-up angiographic examinations for at least 9 months. Classical ICGA signs were recorded at onset and followed for at least 9 months and were correlated with treatment levels. The treatment consisted of high-dose oral corticosteroids (0.8–1.5 mg/kg) preceded by pulse intravenous methylprednisolone (500–1000 mg) for 3 days in hyperacute cases and followed by very slow tapering with the addition of an immunosuppressive agent in cases of insufficient response.

Results The major ICGA signs that were both consistently present and easy to record in the four VKH patients having an acute initial uveitis episode with a pre-treatment angiography and an angiographic follow-up for a minimum of 9 months include (1) early choroidal stromal vessel hyperfluorescence and leakage, (2) hypofluorescent dark dots, (3) fuzzy vascular pattern of large stromal vessels and (4) disc hyperfluorescence. All patients were treated with high-dose inflammation suppressive therapy: in two patients, within 14 and 21 days after initial symptoms, respectively, and in the other two patients, within 6 weeks. Hypofluorescent dark dots, the most constant and easily recordable sign, was very prominent in all cases at presentation. A 90% to complete resolution of dark dots was noted in all four patients after 4 months of therapy. The other three major angiographic signs, early choroidal stromal vessel hyperfluorescence and leakage, indistinct fuzzy vessels at the intermediate angiographic phase and disc hyperfluorescence resolved in all cases within 8 weeks or less of high-dose inflammation suppressive therapy. In three of the four patients, dark dots reappeared after a mean of 7.8 ± 2.8 months after onset of therapy when the patients were under a mean corticosteroid dose of 13.2 ± 6.3 mg per day without

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any significant clinical or fluorescein angiographic signs, indicating subclinical recurrence. An increase in the inflammation suppressive therapy again brought about angiographic resolution of choroidal subclinical disease in all cases.

Conclusion Choroidal inflammation shown by ICG angiography can be suppressed completely by initial high-dose inflammation suppressive therapy. However, recurrent subclinical choroidal inflammation is detected at the end of the tapering period in a high proportion of cases. This indicates that, in the absence of an ICGA follow-up, undetected smoldering subclinical disease may persist, thereby explaining the frequently reported evolution towards sunset glow fundus despite an apparently controlled disease. This is a clear indication that VKH disease should be followed by ICG angiography and, in the case of choroidal subclinical reactivation, a reversal of therapy tapering and an extension of therapy duration should be considered.

Keywords Choroiditis · Immunosuppressive therapy · Indocyanine green angiography · Sunset glow fundus · Systemic corticosteroid therapy · Vogt–Koyanagi–Harada disease

Introduction

Vogt–Koyanagi–Harada (VKH) disease is thought to be an autoimmune disease directed against proteins related to stromal choroidal melanocytes [1, 2]. The initial inflammatory events therefore occur at the level of the choroidal stroma, and adjacent structures such as the retinal pigment epithelium and the retina are only involved subsequently and secondarily. Imaging methods that allow the choroidal space to be visualized are consequently highly indicated for the initial evaluation and subsequent follow-up and, occasionally, for the diagnosis of VKH disease. One of the methods currently used to show the choroidal space and thereby to diagnoseVKH disease is ultrasonography [3]. However, for ultrasonography to be able to show choroidal involvement, there must be a certain degree of choroidal thickening, which is only present in disease which has been progressing for some time. Ultrasonography is far from sensitive enough to show early and isolated choroidal foci (granuloma) or the reappearance of foci in recurrent disease. Indocyanine green (ICG) angiography has been shown to be very sensitive, not only in revealing the presence of small choroidal inflammatory foci but also in providing information on the choriocapillaris circulation and on inflammation of the choroidal stromal vessels [4]. As such, ICG angiography has proven to be the ideal method to investigate choroidal disorders as it is sensitive enough to show minimal and often subclinical changes within the choroid [5–8]. In cases of suspected VKH disease that do not have an acute onset, that are seen at a later stage when sub-optimal therapy has already been introduced or that do not show the complete set of signs, the diagnosis of VKH becomes more difficult, and clinicians should not neglect using all available diagnostic means to reach a diagnosis without delay, including ICG angiography [9–11].

In this article, we first summarize the characteristic set of indocyanine green angiographic (ICGA) signs that can be seen in VKH disease based on earlier works [12–14]. Using such an established ICG angiography semiology, the main purpose of the present work was to follow choroidal involvement in VKH patients from the early stage of the disease at the onset of high-dose inflammation suppressive treatment to the time when treatment had been tapered to low doses or had been discontinued.

Review of ICGA signs

Standard ICGA protocol for inflammatory diseases

A standard ICGA protocol for analyzing choroiditis has been designed and reported earlier [15, 16]. The angiographic procedure comprises three main phases: the early phase, up to 2–3 min, which shows superimposed retinal and choroidal large vessels and incipient exudation of the dye through the choriocapillaris into the choroidal stroma; the intermediate phase, at about 10 min, showing maximum choroidal stromal background fluorescence; the late phase, from about 22–28 min onwards, depending on fundus pigmentation, showing wash-out of the dye from the general circulation, with the large choroidal vessels appearing dark against the background stromal fluorescence.

Indocyanine green angiographic signs

Indocyanine green angiographic signs in VKH disease have been identified in the past and are now used for the initial evaluation and follow-up of VKH disease in many centers [17–19]. We arbitrarily subdivided ICGA signs into two classes: main signs, which are estimated to be the most constant as well as the most useful and easy to use for evaluation and follow-up purposes, and minor signs, which are labeled as such because they have been found to be less consistent and/or less useful for studying the evolution of choroidal disease.

Main or major ICGA signs in VKH disease

Early choroidal stromal vessel hyperfluorescence and leakage indicate severe choroidal stromal inflammatory vasculopathy (Fig. 1). This sign is present in acute and severe disease and most often slowly resolves after the initial induction therapy or during the first 3–6 months of therapy, depending on the severity of the choroidal inflammatory vasculopathy.

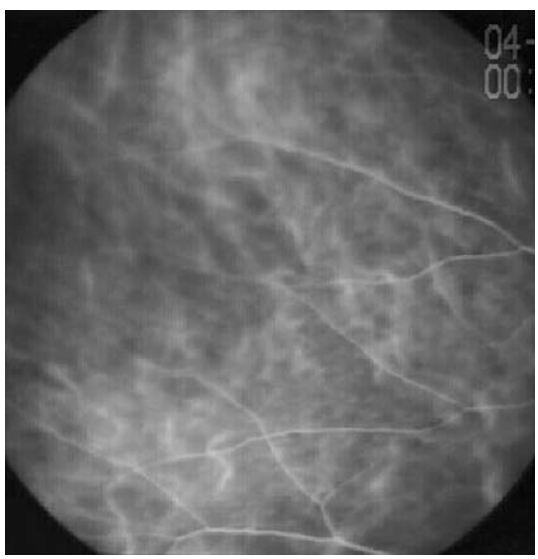

Fig. 1 Early choroidal stromal vessel hyperfluorescence and leakage shown on an early angiographic frame (54 s). Numerous hyperfluorescent choroidal stromal vessels are visible, some of which already have a fuzzy appearance from leakage (*upper area* of picture). This frame has been kindly provided by Drs. T.Kawaguchi and M. Mochizuki, Tokyo, Japan

It appears early in angiography and remains present until removed by diffuse late hyperfluorescence.

Hypofluorescent dark dots, indicating choroidal foci (granuloma), are the most constant and most readily recordable angiographic sign that enables choroidal inflammatory activity to be assessed in a semi-quantitative manner. By correlating the histopathological information available from choroidal sections in VKH disease with ICGA dark dots, it can be hypothesized that the images are generated by the presence of space-occupying lesions (granuloma). These granuloma can be of limited size and therefore not occupying the whole thickness of the choroidal stroma, or the lesions can be large, occupying the whole space from sclera to choriocapillaris. These two types of lesions can be distinguished by ICG angiography and subclassified into two subtypes:

a. *Dark dots present in intermediate phase (8–12 min) and becoming isofluorescent in the late phase*. This pattern indicates the presence of small, partial thickness inflammatory foci (granuloma) (Fig. 2a, b).
b. *Dark dots present up to the late phase (from 20–22 min onwards).* This pattern indicates whole thickness, large choroidal stromal foci (granuloma). The latter type of lesions can also cause additional choriocapillaris non-perfusion, a second cause of hypofluorescence. Obviously, both patterns do co-exist, indicating inflammatory foci of different sizes (Fig. 3a, b)

The presence of hypofluorescent dark dots is the most useful sign for diagnosing subclinical chloroidal disease and for monitoring the effect of therapy. However, it has to be stressed that dark dots do not always mean active granuloma, as they can also signify *stromal scarring*. In the latter case, the dark dots always remain hypofluorescent up to the late phase. The reason for this is believed to be due to the lack of diffusion of ICG molecules within these cicatricial areas as a result of the stroma having shrunk. This phenomenon is seen when acute disease has not been treated adequately because the diagnosis has been delayed, patients have presented late after the onset of symptoms and/or the dosage of early therapy has been insufficient. Fundus photography is usually helpful as it will show dyspigmentation in the hypofluorescent aeas (Fig. 4a). To determine whether persisting dark dots are due to active disease or to

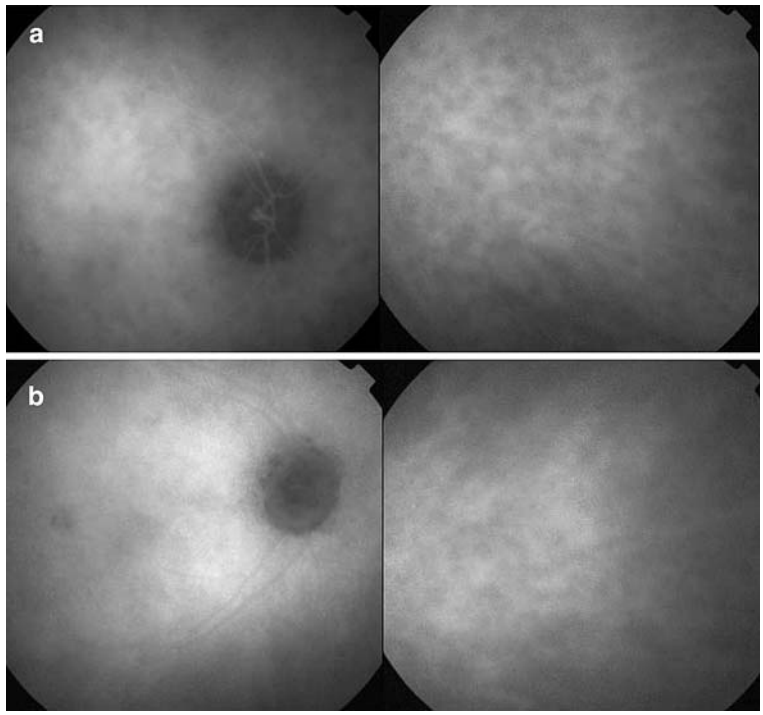

Fig. 2 (**a**) Hypofluorescent dark dots erased at the late angiographic phase (partial thickness choroidal lesions). This frame was taken at the intermediate phase andshows numerous hypofluorescent dark dots in the posterior pole and nasal retina. (**b**)Hypofluorescent dark dots erased at the late angiographic phase (partial thickness choroidal lesions). This frame is of the same area as shown in (**a**) but is taken at the late angiographic phase; many of the hypofluorescent dark are no longer visible because the distribution of indocyanine green (ICG) has been equalized due to the strong exudation of the ICG molecule from larger stromal vessels, thus producing a late diffuse hyperfluorescence

scarring, we usually recommend resuming maximal initial inflammation suppressive therapy, including intravenous methylprednisolone perfusions, for 3 days followed first by oral prednisone (1 mg/kg) for 3–4 weeks and then by a repeat ICG angiography. If there is no evolution or minor decrease in the hypofluorescent areas, the persistent dark dots are probably generated by stromal scars (Fig. 4b).

Fuzzy vascular patterns of large stromal vessels indicate diffuse inflammatory vasculopathy of the stromal vessels. This has to be looked for in the intermediate to late intermediate angiographic phase. In the late phase, this is succeeded by diffuse stromal hyperfluorescence (Fig. 5).

Disc hyperfluorescence. The optic disc usually remains dark and non-fluorescent in a normal ICG angiography. Disc hyperfluorescence indicates very severe disease. It usually regresses rapidly following the initiation of therapy and is therefore a good indicator to use for evaluating response to initial high-dose inflammation suppressive therapy (Fig. 6).

Minor ICG angiographic signs

These signs are either not as regularly found as the major signs or they are of limited use for follow-up purposes.

Disturbance/delay in early choriocapllaris circulation often seen as irregular choriocapillaris filling during the early angiographic phase. (Fig. 7).

Hyperfluorescent pinpoints and exudative subretinal hyperfluorescence. In very acute and severe inflammatory disease, the leaking points at the level of the retinal pigment epithelium seen on fluorescein angiography are also apparent on ICG angiography. In some cases, the subretinal fluid can also be seen on ICG angiography (Fig. 6).

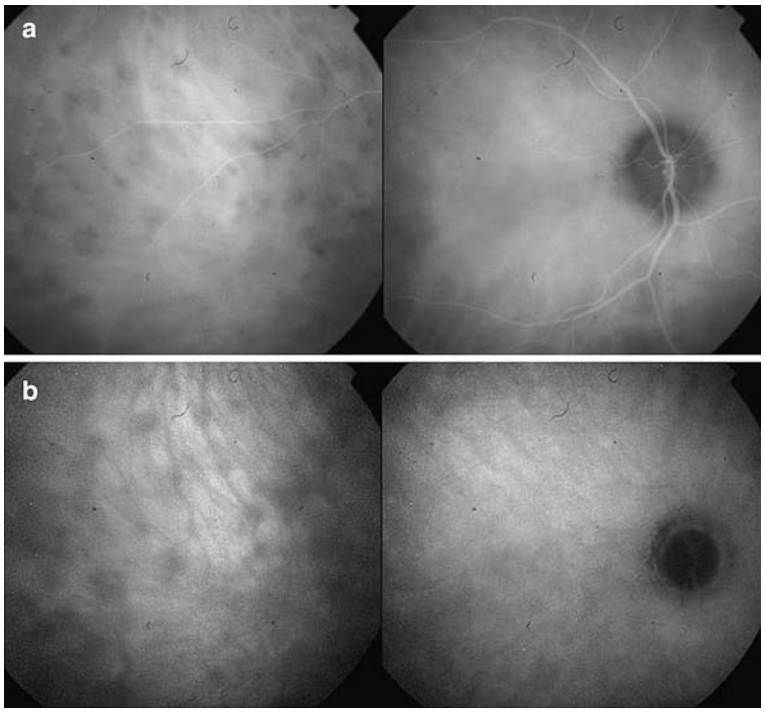

Fig. 3 (**a**) Hypofluorescent dark dots remaining up to the late angiographic phase (full thickness choroidal lesions). This frame was taken in the intermediate phase and shows hypofluorescent dark dots temporal to the macula. (**b**) Hypofluorescent dark dots remaining up to the late angiographic phase (full thickness choroidal lesions). This frame shows the same area as (**a**) taken in the late angiographic phase and shows persistence of hypofluorescent dark dots temporal to the macula

Diffuse late hyperfluorescence. Diffuse late stromal hyperfluorescence is a regular sign in acute and subacute disease, but it is difficult to evaluate with precision as it can be made to be more pronounced when the gain is pushed up in the angiographic system. It is therefore difficult to use it as an evolutional parameter as settings from one angiography to another may be different. (Figs. 5, 7).

This enumeration of ICG signs found in VKH is not exhaustive, and ICG signs are not limited to the ones presented here. However, the ones mentioned are probably the more relevant and the most frequently seen signs.

Patients and methods

Vogt–Koyanagi–Harada patients with an initial acute inflammatory episode in whom a pre-treatment ICG angiography had been performed and who had had an ICG angiographic follow-up of a minimum of 9 months were included in the study. High-dose inflammation suppressive therapy consisted of either pulse intravenous methyprednisolone (500–1000 mg) for 3 days followed by oral corticosteroids at a mean dose of 50 mg or more for the entire first month and a tentative tapering plan over 9–12 months in the absence of recurrence, or oral corticosteroids only, at the same dosage and with the same tapering schedule. In the case of insufficient response, cyclosporine was added to the treatment regimen within the first month.

Standard ophthalmologic examination included the best corrected visual acuity, slit-lamp examination of the anterior segment, fundus examination with fundus photography and laser flare photometry. In cases where subciliary fluid was suspected,ultrasound biomicroscopy was performed. The skin was examined for vitiligo and poliosis, and alopecia were looked for. A spinal tap to search for monopleiocytosis in the cerebrospinal fluid was performed in all patients.

Dual fluorescein and ICG angiography following a standard protocol was performed before the initiation of therapy and then every month ± 10 days during the first 4 months and every 2 months ± 1 month thereafter. Indocyanine green angiographic findings were correlated with clinical findings, fluorescein angiographic signs and with the level of inflammation suppressive therapy. Particular attention was given to the kinetics of the four major ICG angiographic signs: early choroidal stromal vessel hyperfluorescence and leakage, hypofluorescent dark dots, fuzzy pattern of large stromal vessels and disc hyperfluorescence.

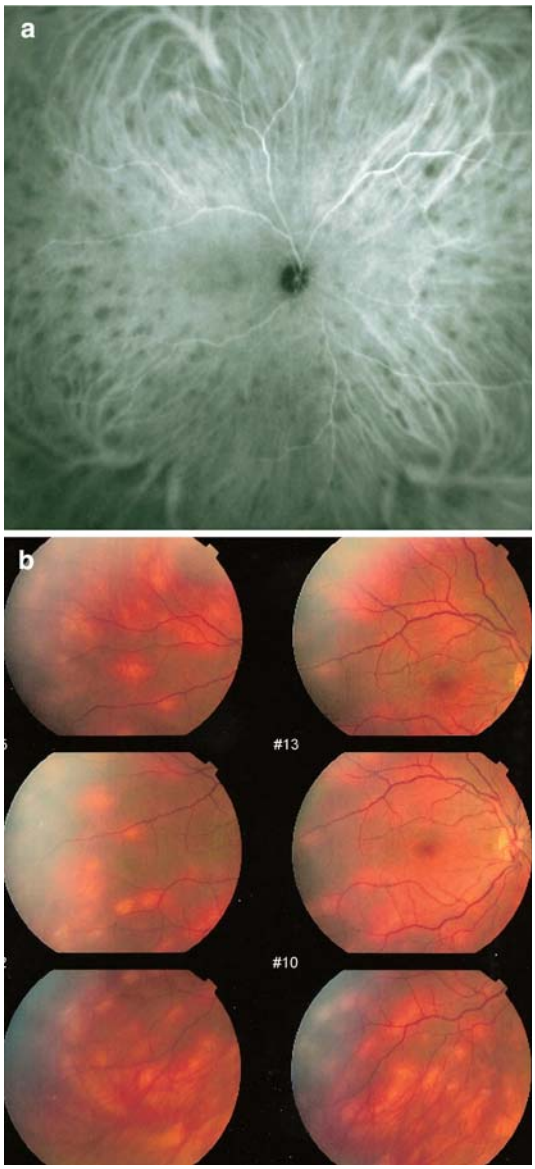

Fig. 4 (**a**) Hypofluorescent dark dots indicating choroidal scarring. Panoramic view of late indocyanine green angiographic (ICGA) phase showing numerous peripheral dark dots 1 week after the initiation of a 3-day intravenous methylprednisolone(1000 mg/day) treatment followed by oral corticosteroids (1.5 mg/kg), a treatment regimen started after the patient had been treated for several weeks with insufficient therapy. Most of the dark dots did not respond to this pulse therapy, indicating that the hypofluorescent areas probably correspond to scarred stromal areas. This was confirmed by the fundus photography (**b**) showing numerous dyspigmented areas. (**b**) Hypofluorescent dark dots indicating choroidal scarring. Fundus photography of the same patient as in (**a**) showing numerous areas of dyspigmentation; these indicate areas of past choroidal inflammation that have led to the loss of pigment and scarring

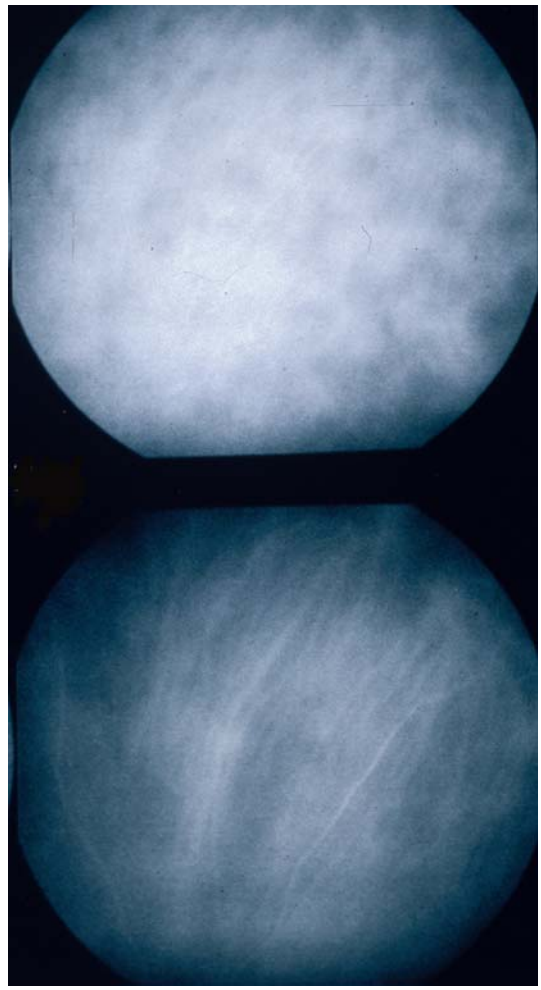

Fig. 5 Fuzzy vessels in the intermediate phase. This is a case of acute posterior recurrence 3 years after the initial episode of Vogt–Koyanagi–Harada disease treated with high-dose inflammation suppressive therapy. *Top* The choroidal stromal vascular pattern can no longer be distinguished, and the whole area is diffusely hyperfluorescent around numerous hypofluorescent dark dots. *Bottom* The same area is shown only 1 week after high-dose inflammation suppressive therapy, including pulse intravenous methylprednisolone (1000 mg/day) for 3 days followed by oral corticosteroids (1.2 mg/kg). There has been resolution of most of the hypofluorescent dark dots and there is a quasi-normal appearance to the choroidal stromal vascular pattern

Results

Patients, disease characteristics and treatments

From 1995 to 2006 a total of 21 VKH patients were seen in the uveitis clinic of the Centre for Ophthalmic Specialized Care (COS), La Source, Lausanne. Four

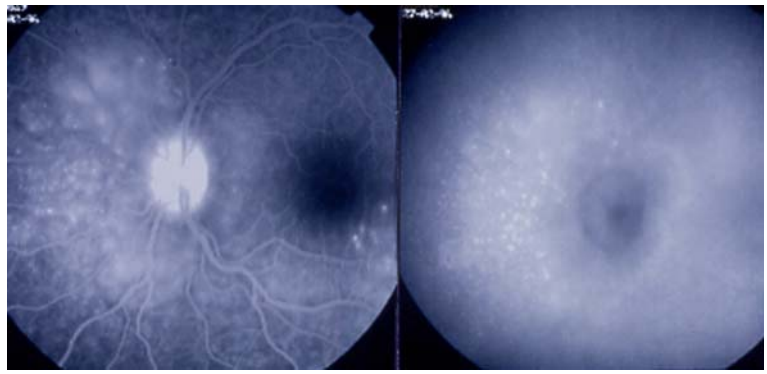

Fig. 6 Hyperfluorescent pinpoints, subretinal ICG dye pooling and disc ICG hyperfluorescence. Hyperacute episode of VKH showing exudative retinal detachment and hyperfluorescent pinpoints on fluorescein angiography (*left*). Due to the severity of the inflammation, leakage points (hyperfluorescent pinpoints) can also be seen on the ICG angiography as well as pooling of fluid under the retina, all of which adds to the diffuse stromal hyperfluorescence. The *left picture* also shows ICG disc hyperfluorescence, a consistent ICGA sign in acute VKH episodes

patients qualified for the study having had a pre-treatment ICG angiography and a regular ICGA follow-up of a minimum of 9 months. The acute episode was treated with high-dose inflammation suppressive therapy within 14–21 days of initial symptoms in two patients (patients 1 and 2) and within 6 weeks for the two other patients. The disease was clinically bilateral for all patients, with the exception of patient 3, whose involvement of the right eye could only be detected by ICG angiography showing all four major signs. Lumbar puncture showed lymphopleiocytosis in all four patients.

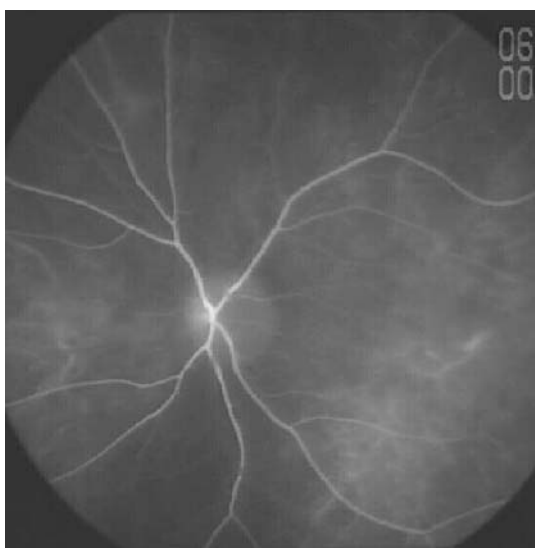

Fig. 7 Choriocapillaris filling delay. The picture taken 26 s after dye injection shows a geographic hypofluorescent area going across the whole fundus from nasal inferior to superior, indicating a delay in the filling of the choriocapllaris. Nasally and in the macular area, two hyperfluorescent stromal vessels can be seen, indicating inflammatory stromal vasculopathy. This frame has been kindly providedby Drs. T. Kawaguchi and M. Mochizuki, Tokyo, Japan

Two patients (patients 1 and 2) had pulse intravenous methyprednisolone (500–1000 mg) for 3 days followed by oral corticosteroid therapy at a mean dose of 50 mg or more for the entire first month and a tentative clinically guided tapering plan over a period of 9–12 months provided there was no recurrence. Two patients (patients 3 and 4) had only oral corticosteroids at the same dosage and the same tapering schedule. Cyclosporine was added to the treatment regimen within the first month for two patients.

Clinical findings at presentation

The mean best corrected visual acuity at presentation was 0.8 ± 0.26. Initial anterior involvement was present in three of the four patients (five eyes), with a mean flare measured by laser flare photometry of 113 ± 210.7 ph/ms. Exudative retinal detachments were present in three of the four patients (five eyes), and papillitis was present in all patients.

Fluorescein angiographic findings at presentation

Fluorescein angiography showed disc hyperfluorescence in all four patients, exudative retinal

detachments in three patients (five eyes) and irregular mottled background fluorescence in all four patients (seven eyes).

Indocyanine green signs at onset and evolution of ICGA findings

Disc hyperfluorescence was present in all patients and was the first sign to resolve – within 2 months – after high-dose inflammation suppressive therapy was started.

Early choroidal stromal vessel hyperfluorescence and leakage were present in three patients and resolved within 3 months after the introduction of high-dose inflammation suppressive therapy. Indistinct fuzzy choroidal stromal vessels in the intermediate angiographic phase was also a constant sign and had resolved in all patients 3 months after the initiation of high-dose inflammation suppressive therapy.

The last angiographic sign to resolve was hypofluorescent dark dots. A 90% resolution of these dots was obtained in all cases within 4 months following the initiation of high-dose inflammation suppressive therapy.

During the tapering of corticosteroid therapy, choroidal disease recurred in the form of the reappearance of hypofluorescent dark dots accompanied by the fuzziness of choroidal vessels in three of the patients after a mean of 7.83 ± 2.84 months. At this time, the afflicted patients were under a mean corticosteroid dose of 13.16 ± 6.33 mg/day, with one patient also receiving 200 mg of cyclosporine. Neither disc hyperfluorescence nor early hyperfluorescent and leaking choroidal stromal vessels recurred during the relapse of choroidal inflammation. Choroidal rebound inflammation occurred in clinically quiet eyes and in the absence of noticeable fluoroscein angiographic signs. This rebound choroidal inflammation during therapy taper was successfully treated in all patients. In patient 1, oral steroid doses were re-increased, cyclosporine was maintained and mycophenolate mofetyl was added as a third immunosuppressive drug; at the last follow-up 20 months after disease onset, the patient was recurrence free but still under therapy. In the second patient, corticosteroid therapy was increased from 7.5 mg per day to 30 mg. This patient was subsequently successfully retapered without a recurrence of choroidal inflammatory foci (hypofluorescent dark dots) and, after a treatment period of 17 months, has been treatment free for 5 months. The third patient presented a more intense recurrence of choroidal inflammation and was managed by intravenous pulse methylprednisolone therapy followed by high-dose oral corticosteroid therapy in combination with cyclosporine. The evolution was characterized by several posterior recurrences or panuveitis that necessitated the continuation of a combination corticosteroid and cyclosporine therapy for an additional 8 years. Treatment was complicated by bilateral hip necrosis requiring a bilateral hip replacement. The patient has now been treatment free for 2 years.

Discussion

The most constant and most relevant ICG angiographic signs for follow-up purposes were hypofluorescent dark dots, which were found in all patients at presentation. This sign most probably represents choroidal inflammatory foci. High-dose inflammation suppressive therapy cleared up these dark dots in all eyes within approximately 4 months. All other accompanying signs, including early hyperfluorescent and leaking choroidal vessels, fuzzy vessels in the intermediate phase and disc hyperfluorescence, resolved even earlier than the hypofluorescent dark dots. This is understandable as the latter signs are the expression of a disturbed vascular permeability and, therefore, they respond much more readily to treatment in comparison to inflammatory foci comprising accumulated cells infiltrating the stromal space. The clearance of a granuloma quite clearly takes much longer than the resolution of abnormal vessel permeability. Surprisingly, the recurrence of hypofluorescent dark dots took place in 75% of our patients (three of the four), even while the patients were still under low-dose corticosteroid therapy (as well as additional cyclosporine in one patient) and in the absence of clinical disease and/or fluorescein angiographic signs. It would appear that in a majority of cases inflammatory lesions redevelop as soon as the treatment is no longer at the threshold necessary to control the autoimmune process. Only the use of ICG angiography made it possible to demonstrate the recurrence of choroidal inflammatory lesions as the latter were silent clinically and were not revealed by

fluorescein angiography. Thus, only ICG angiography was able to prove that such subclinical disease was responsive to increased inflammation suppressive therapy.

These findings raise several questions. Until recently it has not been possible to monitor small-sized choroidal lesions in VKH disease as no method was sensitive enough to detect lesions that did not cause disturbance to neighboring structures. Therefore, any attempt to determine whether the disease was under control was only based on clinical examination, which when normal was taken to indicate no inflammatory activity, and the same was true for fluorescein angiography. With the availability of ICG angiography we now have a method sensitive enough to detect silent inflammatory activity that seems to be present in a large proportion of patients for whom disease was thought to be under control. These findings without a doubt provide the answer for the unexplained high proportion of VKH cases that progress towards sunset glow fundus despite the fact that the disease seemed to be clinically quiet. Indeed, the very high frequency of sunset glow fundus reported from all over the world reaches proportions as high as 89% in Turkey [20], 93% in Japanese patients with chronic inflammation [21] and 95.8% in China [22]. Many authors have tried to find an explanation for the irremediable progression of disease towards sunset glow fundus even in the absence of manifest clinical disease, and some have correlated sunset glow fundus with central nervous system involvement or inflammatory disease activity [21, 23]

However, it would be more sensible to correlate sunset glow fundus with choroidal inflammatory disease activity and link it directly to this factor. Based on our data, we suggest that most cases of VKH disease are under-treated,as subclinical disease recurred in a high proportion of our cases despite the fact that very high-dose and prolonged inflammation suppressive treatment had been given.

We recommend a ICGA-guided follow-up for all VKH patients in order to better fine-tune the therapy and to be in a better position to possibly re-increase therapy as soon as subclinical choroidal recurrence of the disease is detected. Such a precise follow-up could be correlated to an objective pixel analysis of the fundus [24]. This approach may enable clinicians to avoid the fatal evolution of disease towards sunset glow fundus, which has been reported in most studies. On the other hand, such an improved management may change the behavior of the disease. At present, most of the recurrences of the disease are characterized by anterior uveitis as most of the choroidal pigment has been lost early in disease. The use of optimized ICG angiography-guided therapy may increase the probability of posterior recurrences as the optimal treatment will hopefully have preserved most of the choroidal pigment. The number of patients in this study was small, and our results need to be substantiated in a prospective study consisting of a larger number of patients.

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