CLINICAL STUDY

Long-term assessment of combined vitamin A and E treatment for the prevention of retinal degeneration in abetalipoproteinaemia and hypobetalipoproteinaemia patients

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Abstract

Purpose **To assess the long-term efficacy of combined vitamin A and E treatment in preventing retinal degeneration in patients with abetalipoproteinaemia (ABL) or homozygous hypobetalipoproteinaemia (HBL).**

Methods **Ten patients with ABL and 3 with homozygous HBL who were treated with oral supplements of vitamins A and E were studied. Systemic, ophthalmological and electroretinographic follow-up for a mean of 11.7 years (range 4–20 years) after onset of treatment was evaluated.**

Results **Despite vitamin A and E treatment, 7 of 10 patients who began treatment prior to 2 years of age and all 3 patients who began treatment later in life manifested unusual fundoscopic pigmentary changes over time. At the end of follow-up, 11 of 13 patients had subnormal mixed cone-rod electroretinogram amplitudes. Seven of 10 patients for whom perimetry was available had mild to severe constriction of the visual fields.**

Conclusions **Combined oral vitamin A and E supplementation that is initiated prior to 2 years of age can markedly attenuate the severe retinal degeneration that is associated with untreated ABL or homozygous HBL. Yet, fundoscopic and functional retinal changes do occur despite early initiation of vitamin treatment. Therefore, the adequacy of the present treatment protocol for ABL and homozygous HBL should be re-evaluated.**

Key words Abetalipoproteinaemia, Hypobetalipoproteinaemia, Retinal degeneration, Vitamin A, Vitamin E

Abetalipoproteinaemia and homozygosity to hypobetalipoproteinaemia are two distinct genetic entities that results in the complete absence of apolipoprotein B (apo-B) from the blood. Chylomicrons, very low density lipoproteins (VLDL) and low density lipoproteins (LDL) are not formed and, consequently, levels of cholesterol and triglycerides are extremely low and the absorption of lipid-soluble vitamins (vitamin A, E and K) is impaired.

Abetalipoproteinaemia (ABL), or Bassen–Kornzweig syndrome,[1] is a rare autosomal recessive disorder that is caused by an abnormality in a microsomal triglyceride transfer protein normally present in liver and intestine.[2–4] Homozygosity to hypobetalipoproteinaemia (HBL) is similar to ABL in terms of signs, symptoms and laboratory findings. However, the genetic basis is different. HBL represents a heterogeneous group of genetic defects. At least 25 mutations in the apo-B gene have been described in association with this disease. Accordingly, the level, composition and function of apo-B containing lipoproteins differ among various kindred.[5] Ocular manifestations in ABL and HBL usually appear in childhood: ophthalmoplegia, ptosis, nystagmus, strabismus and angioid streaks have been reported.[6–11] However, the most distinct ocular manifestation is a retinal degeneration that was described as retinitis-pigmentosa (RP)-like. Patients can show pigmentary retinopathy that frequently involves the macula early on with a reduction in visual acuity. Nyctalopia and constricted visual fields are common, and the electroretinogram is markedly reduced or extinct.[12–14]

To try to avoid the severe sequelae of ABL and homozygosity to HBL, early treatment with oral supplementation of the lipid-soluble vitamins A and E has been advocated by our group[15,16] and by others.[17] The initial report by Bishara *et al.*[15] included 2–6 years of follow-up of 8 ABL patients. At that time, all patients who began treatment at an early age and who were

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Table 1. *Patient characteristics, visual fields and electrophysiological testing*

Patient no.	Age/Sex	Disease	Therapy onset	Clinical signs at diagnosis	VA at FU (OD/OS)	VF	ERG (b wave in μV) Cones	ERG (b wave in μV) Rods	Fundus at FU	EOG (in %)	FU (years)
Group A											
1	7M	ABL	20 mo	Malabsorption	6/9, 6/9	ND	78	–	T	–	4
2	7M	ABL	Birth	N	6/6, 6/6	ND	195	293	N	246	7
3	10M	ABL	12 mo	Malabsorption	6/6, 6/6	N	145	230	N	250	9
4	14M	ABL	10 mo	Malabsorption	6/7.5, 6/7.5	N	150	100	N	–	13
5	18M	ABL	7 mo	Malabsorption	6/7.5, 6/7.5	C	152	258	T	214	18
6	18M	ABL	Birth	N	6/7.5, 6/7.5	ND	180	195	T	250	18
7	21F	ABL	18 mo	Malabsorption, ataxia	6/7.5, 6/7.5	C	140	308	PR	244	18
8	22M	ABL	24 mo	Malabsorption	6/6, 6/6	N	230	383	T	220	20
9	17F	HBL	12 mo	Malabsorption	6/12, 6/9	C	113	273	N	200	15
10	18F	HBL	12 mo	N	6/6, 6/6	C	70	70	N	230	9
Group B											
11	22F	ABL	11 yr	Malabsorption, ataxia	6/12, 6/12	C	Extinct	Extinct	PR	150	11
12	36M	ABL	26 yr	Malabsorption, ataxia, neuropathy	6/12, 6/12	C	70	80	PR, T	140	10
13	23F	HBL	5 yr	Malabsorption	6/6, 6/6	C	Extinct	Extinct	PR	140	18

Age, age at last follow-up examination in years; F, female; M, male; mo, months; yr, years; ABL, abetalipoproteinaemia; HBL, hypobetalipoproteinaemia; N, normal; T, exaggerated tigroid; PR, pigmentary retinopathy; VF, Goldmann visual field; C, constricted visual field; ND, not done; N, normal; VA, visual acuity; FU, follow-up; ERG, electroretinogram at last follow-up examination (b wave amplitudes are presented; lower limit of normal for the cone response is 90 μV, for the rod response 200 μV); EOG, electro-oculogram Arden ratio at last follow-up examination (lower limit of normal = 180%).
In general, ocular findings were symmetrical between the two eyes. The VF, ERG and EOG of the better eye are presented.

the ones expected to benefit most from the treatment, were younger than 10 years of age. As the retinopathy of ABL often manifests at the end of the first decade or even later, it was not possible to determine the efficacy of vitamin treatment for a prolonged period. Presently, only one other study, which also included 8 patients, has addressed the question of the long-term efficacy of vitamin treatment started at an early age.[17]

The present report serves to extend our observations on 6 patients included in the original study[15] on which an average follow-up of 15.8 years since onset of treatment is now available. In addition, clinical and electroretinographic findings in 4 other ABL patients, as well as in 3 homozygous HBL patients, are presented. To the best of our knowledge, this comprises the longest follow-up of ocular involvement in ABL patients treated by vitamin supplementation and the first report to include long-term observations in treated homozygous HBL patients.

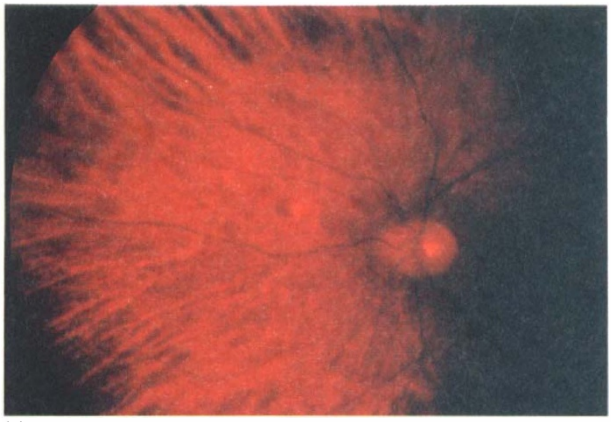
Patients and methods

Patients

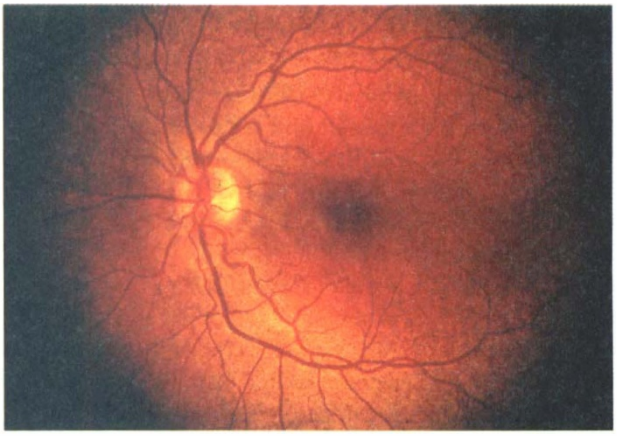
We sequentially evaluated 10 ABL and 3 homozygous HBL patients. Diagnosis of ABL and homozygous HBL was based on typical clinical findings (Table 1), and confirmed by characteristic lipoprotein and apo-B levels in the blood. The two conditions were separated by performing lipid studies in the parents of the patients (parents of ABL patients show normal levels of apo-B-containing lipoproteins whereas parents of homozygous HBL patients show decreased levels). All patients received oral treatment with vitamin A 15 000 units per day and vitamin E 100 mg/kg per day, initiated immediately following diagnosis. A low-fat diet with supplementation of medium-chain fatty acids was recommended. Follow-up included repeated physical and ophthalmological examinations, electroretinograms and electro-oculograms. In 10 of the 13 patients kinetic and/or static perimetry was also available. Plasma vitamin A and E levels as a measure of efficacy and compliance with treatment were performed, and in 2 patients, vitamin E levels in adipose tissue biopsy were available.

Electroretinogram (ERG) and electro-oculogram (EOG)

ERG was performed as described in detail elsewhere.[18] In short, full-field ERGs were recorded using corneal electrodes (Henke's type), a Cyberscan 4000 computerised system (Microshev, Efrat, Israel) and a Grass PS22 Photostimulator (Quincy, MA). The forehead served as reference and the ear as ground. In the dark-adapted state, two responses were acquired: a rod response to a dim blue flash using a Wratten 47b filter (Kodak, Rochester, NY) and a mixed cone-rod response to flashes of white light (2.75 lumen × second/foot^2). In the light-adapted state, a background light of 20 foot candelas was used to suppress rods, and the cone response to flashes of white light (11 lumen × second/foot^2) presented at 1 Hz was acquired. All ERG responses were signal averaged ($n = 4$). With this method the minimal normal values in our laboratory for adults are 400 μV for the scotopic mixed cone–rod b wave, 200 μV



(a)



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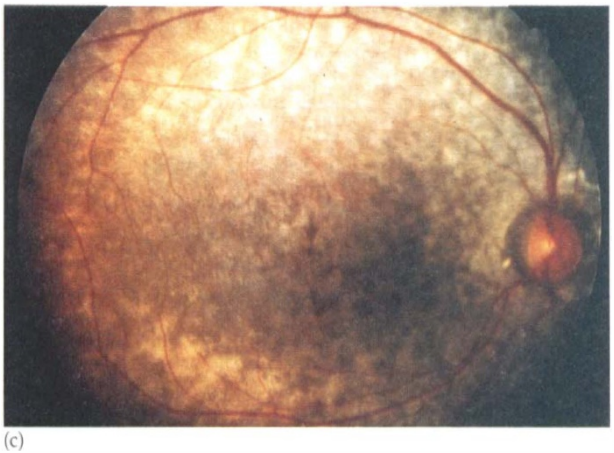

(c)

Fig. 1. *Colour fundus photographs. (a) Patient 6 at the age of 17 years showing a tigroid fundus pattern that does not match the fair complexion of the patient. (b) Patient 7 at the age of 20 years showing 'salt and pepper' retinopathy in which the whitish component predominates. This patient started vitamin therapy at the age of 18 months. (c) Patient 13 at the age of 20 years showing 'salt and pepper' retinopathy. Note that the degree of retinopathy is more severe in this patient, who began treatment at the age of 5 years.*

for the scotopic blue rod b wave, and 90 μV for the photopic cone b wave. Some of the ERGs were performed prior to introduction of the international ISCEV standards. However, the white flash used in the dark-adapted state is within the range specified by the standard so that responses may be comparable.

EOGs were performed using bilateral skin electrodes on both canthi and an HP 7402A chart recorder (Hewlett Packard, Corvalis, OR). The Arden ratio was derived according to the accepted protocol.[19] The lower level of normal under our conditions is 180% light peak/dark trough ratio.

Results

Patient characteristics, electrophysiological and visual field results are presented in Table 1. Two to six years of follow-up of patients numbered 5–10 in Table 1 were previously reported by Bishara *et al.*[15] (patients 1, 2, 4–7 in Bishara *et al.*'s report).

We classified our patients into two groups according to the age at which treatment was initiated. Group A included 8 ABL and 2 HBL patients in whom vitamin therapy was started before the age of 2 years. In this group, 4 of 6 patients older than 17 years and 1 patient aged 6 years had fundoscopic changes that can best be

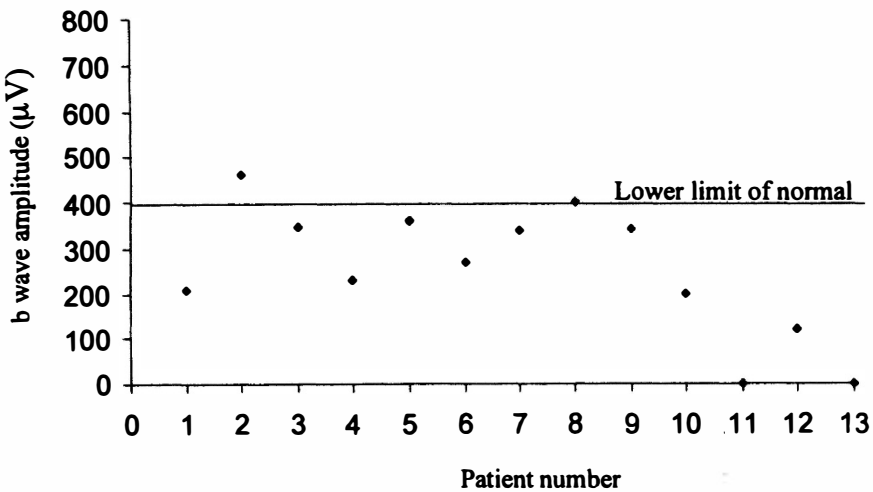

Fig. 2. *The dark-adapted mixed cone–rod b wave amplitude of group A patients (numbers 1–10) and group B patients (numbers 11–13) at the end of follow-up. The lower limit of normal for this response (mean –2 SD) under our testing conditions is 400* μV.

described as an 'exaggerated tigroid fundus' (Fig. 1a). The macula was fundoscopically normal in all patients in this group. One patient also had pigmentary retinal changes in the form of 'salt and pepper' retinopathy in which the whitish component predominated (Fig. 1b). None of the patients had the 'RP-like' pigmentary changes described previously in both treated and untreated ABL patients.

Eight of the 10 patients in group A had mild to moderate reduction of the scotopic mixed cone–rod b wave at the end of follow-up (Fig. 2). The scotopic rod ERGs were more affected than the cone ERGs (Table 1). Four of the 7 patients in this group for whom perimetry was available demonstrated mild constriction of the visual fields (40°–50° on the Goldmann V4e isopter).

In contrast to the ERG results, 9 of the 10 patients had a normal EOG, and at the end of follow-up all patients in group A were free of the neurological or systemic complications that are usually associated with untreated ABL and HBL.

Group B included 2 ABL patients and 1 HBL patient in whom vitamin supplementation was initiated at the ages of 11, 26 and 5 years respectively. One patient manifested RP-like fundus changes; the second patient showed small mid-peripheral chorioretinal scars, diffuse retinal pigment epithelium atrophy and mild narrowing of the arteries; while the third patient had 'salt and pepper' retinopathy in which the whitish component predominated (Fig. 1c). All 3 patients had severe constriction of the visual fields and low EOG Arden ratios (140–150%, Table 1). A markedly reduced ERG that was stable under vitamin treatment for 10 years was observed in one patient (no. 12), while ERGs deteriorated despite treatment in the 2 other patients of this group (nos. 11, 13) until they were non-recordable at the last available ERG examination (Fig. 2). Two patients had ataxia and 1 also had peripheral neuropathy. However, under vitamin treatment these neurological complications did not seem to progress.

During follow-up, blood levels of beta-carotene were between 15 and 151 mg/100 ml in all patients (normal: 20–500 mg/100 ml), and vitamin E levels were between 0.03 and 0.35 mg/100 ml in all patients (normal: 0.5–1 mg/100 ml). Adipose tissue biopsy performed in patients 3 and 7 revealed normal vitamin E levels. None of the patients in the present study had side-effects related to vitamin A toxicity, and this is to be expected considering the relatively low vitamin A blood levels. However, it should be mentioned that in our previous report[15] 1 of the patients had pseudotumour cerebri that was attributed to vitamin A toxicity. Treatment was discontinued and subsequently this patient was lost for follow-up.

Discussion

ABL and homozygosity to HBL are considered to be rare instances in which appropriate treatment can prevent or delay progression of a retinal degeneration. The basis for combined vitamin A and E treatment in these patients stems from both clinical and laboratory data: since untreated ABL and homozygous HBL patients have extremely low vitamin A and E blood levels and as vitamin A plays a crucial role in phototransduction, it is within reason to expect that replacement therapy with vitamin A may be beneficial in these patients. Evidence also exists that vitamin E is important for normal retinal function. Deficiency of vitamin E can cause retinopathy in the dog, rat and monkey.[20–22] In humans, deficiency of vitamin E in several disease states was found to be associated with retinal degeneration and visual field constriction.[23] Furthermore, Robison *et al.*[22] demonstrated that combined deficiency of vitamin A and E in the rat can cause synergistic impairment of retinal function.

Clinical data on the efficacy of vitamin supplementation in ABL was initially collected in the early 1960s. At the time, ABL patients were treated by high oral or intramuscular doses of vitamin A alone. Variable short-term success in slowing progression of retinal disease, improving dark adaptation, and in regaining recordable ERG responses in patients that previously had extinct ERGs were reported. However, some ABL patient did not respond to vitamin A treatment, and in those who did, the protective effect of vitamin A on the retina was temporary.[24–26]

Although ABL patients have been receiving combined vitamin A and E treatment since the early 1960s, only a small number of reports have addressed the question of intermediate and long-term benefits of this treatment. Muller and associates and Runge and associates[17,27–29] described in detail the long-term follow-up of 7 ABL patients and 1 homozygous HBL patient who received combined vitamin A, E and K therapy, while maintaining a low-fat diet. In their most recent publication in 1986,[17] 12–18 years of follow-up of 6 patients aged 13–26 years was reported. Four of these 6 patients had some degree of abnormal retinal pigmentation or pigment mottling, despite the fact that 2 of them began vitamin treatment prior to the age of 2 years. One of the patients also had constriction of the visual fields. However, in Runges' report, at the end of follow-up all patients had normal ERGs. In addition, the progression of both the retinal degeneration and the neurological deficts halted under vitamin A and E treatment in all patients. Therefore, the authors concluded that such treatment could prevent retinal and neurological manifestations of ABL. Another group of 10 ABL patients, on whom electrophysiological and clinical follow-up of up to 3 years was available, was reported in 1986 by Brin *et al.*[30] Six of 7 patients who underwent ERG testing had abnormal ERG responses. It is important to note that all patients in this report, except one, were older than 19 years at the time of first examination. One patient was 3 years old at the time of the first ERG examination and he too had subnormal responses. Over the 3 years of follow-up the authors did not see progressive retinal degeneration in patients with normal vitamin A levels on adequate supplementation of vitamin E. The authors concluded that replacement

therapy with vitamin A and E can stabilise or improve neurological and ophthalmic lesions that are associated with ABL.

In 1982 our group reported on 8 ABL patients with a follow-up of 2–6 years.[15] Seven patients who received combined vitamin A and E treatment had stable ERG amplitudes. In the 4 patients in whom treatment was initiated before 2 years of age, the fundi were normal and the ERGs stable throughout the follow-up period. However, these 4 patients were less than 5 years old at the end of follow-up. Three of the patients reported began treatment after the age of 8 years at a time when ERG amplitudes were already reduced. Under treatment, retinal degeneration did not progress, but the ERG did not return to normal values.

Data on the retinal degeneration that is associated with HBL, and on its treatment by fat-soluble vitamins, is very limited. One of the patients in Runge's report had homozygous HBL and responded well to vitamins A and E. Three other HBL patients, 2 of them heterozygous with mild retinal changes, and 1 homozygous with RP-like disease, were reported by Yee *et al*. However, the efficacy of vitamin treatment was not evaluated in that report.[7]

Our previous report with 2–6 years of follow-up showed preservation of retinal function under vitamin treatment.[15] However, in that report, patients who began receiving therapy prior to 2 years of age were still young at the end of the study. In contrast, at the end of the present study, with longer follow-up, subnormal ERG amplitudes were observed in the majority of patients, even after receiving high oral doses of vitamin A and E from prior to 2 years of age. In addition, many had an abnormal fundus appearance and constriction of the visual fields. These abnormalities in older ABL and HBL patients were probably not witnessed by Bishara *et al*.[15] due to the young patient age at that time. Our findings also differ from those described by Runge *et al*.[17] It is interesting that although 2 of their patients began vitamin supplementation therapy at the relatively late age of 7 years, ERGs were normal in all their treated patients. Yet, in that report, 1 patient did have constricted visual fields and in 2 patients pigmentary changes were noted despite initiation of vitamin therapy prior to 2 years of age. Since the treatment protocol and timing of treatment initiation are similar, the discrepancy between our study and that of Runge *et al*. is difficult to reconcile.

From our experience, and as might be expected, patients who begin receiving vitamin therapy at an older age have a markedly worse prognosis than those who start treatment earlier. Indeed, 2 of our 3 patients in group B who began treatment at the ages of 5, 11 and 26 years showed progression of retinal degeneration despite treatment. Although previous reports are in accordance with those findings,[15,30,31] others have reported normalisation of the ERG even when treatment was initiated in patients in their teens.[17]

How can the occurrence of retinal changes under vitamin therapy be explained? It is conceivable that vitamins A and E are deficient in target tissues despite high-dose oral supplementation. Generally, a dose of 100 mg/kg per day of orally administered vitamin E is advocated.[16] Despite these high doses, serum vitamin E levels in previous reports, as well as in our patients, rarely exceed one half of the normal values.[15,17] These low levels of vitamin E are expected since vitamin E in plasma has no specific carrier and is transferred mainly by the triglyceride-rich lipoproteins VLDL and LDL that are absent in ABL patients. Despite low serum levels, tissue levels of vitamin E may be adequate. Therefore, adipose tissue biopsies were performed in 2 of our patients. In both cases vitamin E levels were normal. Serum levels of vitamin A, unlike those of vitamin E, accurately reflect the adequacy of treatment. In most of our patients vitamin A levels were within the normal range throughout the study period. A few patients intermittently had mildly subnormal vitamin A levels, but no correlation was found between vitamin A or E levels and severity of fundus changes, visual field constriction or ERG amplitudes. However, since testing of levels reflects only isolated time points, it is still possible that our patients did experience transient vitamin A or vitamin E deficiencies between tests that were sufficiently low and prolonged to cause retinal changes.

Alternatively, the retinal abnormalities in our patients may be the result of a deficiency of factors, other than fat-soluble vitamins, that are perhaps important for normal retinal function. Essential fatty acids may play a role in retinal dystrophies. Abnormalities in fatty acid metabolism were found in RP patients and may contribute to the retinal pathology in these patients.[32–34] In ABL patients, low levels of linoleic acid in plasma and in red blood cell membranes have been reported.[35] In addition, 2 ABL patients who received supplementation of polyunsaturated fatty acids were reported to have favourable neurological outcome.[27] Therefore, it is possible that patients are lacking specific fatty acids or other nutrients that are essential for preservation of normal retinal function.

It should be noted that our case-series study design is not ideal for assessment of treatment efficacy due to the lack of a control group, among other reasons. There is ample evidence that without treatment a very severe retinopathy (and neuropathy) ensues in ABL and HBL patients.[12–14] Hence, vitamin supplementation that since the early 1960s has been known to be effective, is offered once diagnosis is made. It is rare to find untreated patients (other than very young ones) and we did not follow any such cases. Under these conditions, the only applicable study design is a case-series with comparison with normal controls and reference to the historical evidence of severe impairment in patients prior to the vitamin-treatment era.

We conclude that although long-term treatment with vitamin A and E, especially when begun at an early age, can significantly attenuate ophthalmic manifestations associated with ABL and homozygous HBL, retinal changes still occur. Pigmentary changes, constriction of visual fields and decreased ERG amplitudes may

progress at an older age and result in significant functional impairment. Hence, more studies are needed in order to define the cause of the mild retinal degeneration noted in ABL and homozygous HBL patients while under vitamin A and E treatment. Further follow-up is required to assess whether the trend observed towards worsening of retinal function is indeed progressive; if it is, additional treatment modalities should be considered.

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