Use of an Arginine-Restricted Diet to Slow Progression of Visual Loss in Patients With Gyrate Atrophy

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**Objective:** To quantify the effect of long-term reduction of plasma ornithine levels through adherence to an arginine-restricted diet on visual function in patients of all ages with gyrate atrophy of the retina and choroid.

**Methods:** A long-term observational study was conducted on 27 patients with gyrate atrophy, 17 of whom elected to comply with the arginine-restricted diet and 10 who were unable to comply. The mean rates of change in the electroretinogram combined response, electroretinogram flicker response, and kinetic and static perimetry were determined.

**Results:** After mean follow-up of 13.9 years for the patients on the diet and 14.1 years for those not on the diet, the mean rates of change for the diet group compared with those of the no-diet group were statistically significantly slower for all outcome measures (age-adjusted \( P < .05 \)) except for static perimetry (\( P = .06 \)).

**Conclusions:** Adhering to an arginine-restricted diet so as to lower the plasma ornithine level below an average of 5.29 to 6.61 mg/dL (400-500 µmol/L) will slow the loss of function as measured by sequential electroretinography and visual field examinations.


In 1991, Kaiser-Kupfer et al. reported that long-term reduction of plasma ornithine levels slowed the progression of the chorioretinal degeneration in gyrate atrophy (GA) of the choroid and retina. To minimize variables such as genotype at the disease gene locus, genetic background, compliance with treatment, and age at the time of instituting treatment, 2 sets of sibling pairs (younger than 10 years) were placed on an arginine-restricted diet. When the diet was begun, the younger siblings were aged 2 years 10 months and 2 years 8 months; their older siblings were aged 6 years 4 months and 9 years 4 months, respectively. For each pair, the retina of the younger sibling had minimal changes at the time treatment was begun, while the older sibling had already developed extensive chorioretinal lesions. By the time the 2 younger siblings had both received the diet for more than half their lives and had reached the age at which the older sibling began the diet, the younger siblings had dramatically less ocular involvement than their older siblings at comparable ages.

We have continued to observe the 2 sets of siblings on an arginine-restricted diet. After 16 to 17 years on this diet, the younger sibling in each pair, who had received the diet at an earlier age, manifested a slower progression of chorioretinal lesions than the older sibling. One younger sibling maintained an average plasma ornithine level of 1.55 mg/dL (117 µmol/L), while the other younger sibling maintained an average of 1.84 mg/dL (139 µmol/L) (normal plasma ornithine level is 0.53-1.59 mg/dL [40-120 µmol/L]). Thus, it was concluded that if the diet was started at an early age, long-term reduction in plasma ornithine levels appeared to appreciably slow the progression of the chorioretinal lesions. With respect to retinal function, a moderate gradual decline in sensitivity in the central 30° visual field or a gradual reduction in the amplitude of the electroretinogram combined response was observed.

In an effort to generalize this beneficial treatment effect to a larger, older, and more diverse population of patients with GA, 27 patients who were enrolled in a long-term observational study were analyzed with respect to their clinical course. The purpose of this article is to report observations that suggest that being on a diet with a sustained decrease in plasma ornithine level appears to slow progression of the chorioretinal degeneration in GA.
Twenty-seven patients were enrolled and encouraged to adopt an arginine-restricted diet. At yearly follow-up visits, diet compliance was monitored by self-reporting and plasma ornithine levels were measured. At the same visits, the primary outcome measurements were taken: electroretinogram combined response, electroretinogram flicker response, Goldmann kinetic perimetry, and Humphrey automated static perimetry. Both eyes were tested, but only data obtained from the right eye were used for analysis. At the end of follow-up, patients were individually identified as having adhered to the diet to some degree or as not having followed the diet at all during the study period. Thus, there were 17 patients on the diet who were observed for a total of 236 patient-years and 10 patients not on the diet who were observed for 141 patient-years.

The methods of the primary outcome measures were presented in detail previously. Briefly, the exponential model of change proposed by Caruso et al implies that the log-transformed measures change linearly with time, and the resultant slope is the natural index of rate of change. Slopes for each patient were therefore estimated from the simple linear regression of log (variable) over time in years. The 2-sided hypothesis that there was no mean difference in slopes between these 2 groups (on and off diet) was evaluated by analysis of covariance to adjust for differences in age.

### RESULTS

Table 1 summarizes patient characteristics. Mean follow-up time was comparable between the groups, but the median age of the patients on the diet was younger at the end of the study by about 15 years. The serial plasma ornithine measurements were averaged for each patient, and the resulting means were averaged over the diet groups, weighted by each patient’s follow-up time. By this index, ornithine levels in the off-diet group were twice as high as those in the on-diet group. The female-male ratio was essentially reversed: 14 (82%) of patients on the diet and 2 (20%) not on the diet were female.

The comparisons of primary outcomes are summarized in Table 2. Because the diet groups were discrepant in age, the mean slopes (ie, mean rates of change) of the outcome measures were adjusted for age by analysis of covariance. After adjustment, all were statistically significantly greater for the off-diet group ($P<.05$) except for static perimetry ($P=.06$).

### COMMENT

In previous articles our group reported the beneficial effect of an arginine-restricted diet in 2 pairs of siblings younger than 10 years with GA. Those studies concluded that if the diet was started at an early age, long-term reduction in plasma ornithine levels, especially in younger patients, appeared to appreciably slow the progression of the chorioretinal lesions. With respect to retinal function, progressive loss was slowed but to a lesser extent. These results are consistent with those in a mouse model of GA in which long-term reduction in plasma ornithine level with an arginine-restricted diet prevented retinal degeneration.

Because many patients with GA do not come to medical attention with the correct diagnosis until sometime in the second or third decade of life, it is also important to determine whether sustained reduction of plasma ornithine level at this stage of life has a beneficial effect. To answer this question, we com-
pared the progress of the disease in 2 groups of patients with GA of all ages: those who were able to comply with the diet over several years, with average plasma ornithine levels weighted by length of follow-up of 4.47 mg/dL (338 µmol/L) or about 6 times normal; and those who elected not to go on the diet or were poor compliers, with an average plasma ornithine level weighted by length of follow-up of 9.28 mg/dL (702 µmol/L) or about 10 times normal. As judged by 3 of the outcome measures, the difference between those on the diet and those not on the diet was statistically significant. For the fourth measure, static perimetry, the estimated effect of diet was consistent in magnitude and direction with the other measures; its lack of statistical significance may be due to lack of statistical power.

A limitation of the observational study is the self-selection of the patients into the diet groups. Consequently, there may be other factors that could play a role as confounding variables. Age was one such possible factor, but significant differences between the 2 groups mostly persisted after the effect of age was removed. Although the sex distributions between the groups were markedly disparate, there is no evidence to suggest that the course or severity of GA is influenced by sex. Therefore, the difference in the proportion of women in the group is not likely to have played a role in the outcome of the study. The sex distribution in the 2 groups may merely reflect the fact that in our sample, women were more successful in complying with the diet than men. The ornithine-δ-aminotransferase genotypes of the patients in each group were analyzed and, other than in sibling pairs, no pattern was observed. Finally, the amount of residual ornithine-δ-aminotransferase activity in patients in each group was analyzed and appeared to be randomly distributed in each group. We concluded that adhering to an arginine-restricted diet so that the plasma ornithine level falls below an average of 5.29 to 6.61 mg/dL (400-500 µmol/L) will slow the loss of function as measured by sequential electroretinography and visual field examinations.

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REFERENCES