

## SCIENTIFIC REPORT

# Visual hallucinations and Charles Bonnet syndrome after photodynamic therapy for age related macular degeneration

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**Aims:** To report on visual hallucinations and Charles Bonnet syndrome (CBS) that may occur in patients with age related macular degeneration (AMD) treated by photodynamic therapy (PDT) with verteporfin for choroidal neovascularisation (CNV).

**Methods:** 100 consecutive patients were asked to respond to an orally administered questionnaire on visual hallucinations following PDT. Three groups of patients, respectively without visual hallucinations, with unstructured visual hallucinations, and with structured hallucinations—that is, CBS, were compared by ANOVA, Scheffe's test, or the  $\chi^2$  test, to establish whether age, sex, or visual acuity, as scored on ETDRS charts, are risk factors for the occurrence of visual hallucinations.

**Results:** Five patients (5%) described transient structured visual hallucinations, including known or unknown faces and geometric patterns. Fifteen patients (15%) reported photopsias and flashing lights of various colours. These symptoms usually occurred a few days after PDT. There was no significant difference between the group of patients with structured visual hallucinations and the two other groups, with regard to age ( $p=0.435$ ), sex ( $p=0.406$ ), or visual acuity ( $p=0.835$ ).

**Conclusions:** Visual hallucinations and CBS appear to be a possible, although unrecognised, side effect of PDT for CNV, which occur just after treatment. These results suggest the need to include the possibility of visual hallucinations in the information given to patients before PDT.

Photodynamic therapy (PDT) is a new treatment for choroidal neovascularisation (CNV) that involves an intravenous injection of a photosensitiser or light activated drug. After infusion, the photosensitiser is activated focally by illumination with light from a laser source, at a wavelength that corresponds to the absorption peak of the drug but is not strong enough to create thermal damage.<sup>1</sup> PDT with verteporfin has been found to be effective, and is recommended for the treatment of selected patients with age related macular degeneration (AMD) combined with CNV.<sup>2–4</sup> Randomised clinical trials have shown that PDT with verteporfin was associated with few ocular or systemic adverse events, including transient visual disturbances—that is, abnormal vision, decreased vision, and visual field defects.<sup>2–3</sup> However, to our knowledge, visual hallucinations have not been reported with verteporfin and PDT, although they have been observed in some patients with untreated CNV.<sup>6</sup> Recently, complex visual hallucinations were reported immediately after other treatments of CNV, including macular photocoagulation<sup>7</sup> and macular surgical translocation.<sup>8</sup> Many authors have pointed out that the prevalence of complex visual hallucinations in psychologically normal people, known as the Charles Bonnet

syndrome, was underestimated.<sup>9–14</sup> Patients usually do not spontaneously describe their hallucinations because they are afraid of being thought mentally ill. Specific oral questionnaires should therefore be proposed to patients to evaluate the occurrence of this syndrome. Accordingly, the present prospective study was undertaken to define the nature and incidence of visual hallucinations following PDT.

## PATIENTS AND METHODS

### Patients

One hundred consecutive patients with AMD, with predominantly classic CNV diagnosed by fluorescein angiography were included at the time of their first angiographic study 6–12 weeks after PDT.

At the time of treatment, patients had subfoveal CNV, with a classic component occupying 50% or more of the area of the entire lesion. PDT had been performed before inclusion according to the standardised protocol previously described,<sup>2</sup> using reconstituted diluted verteporfin (Visudyne; Novartis AG, Bülach, Switzerland). Laser (Coherent, Palo Alto, CA, USA) was applied by one of us (GQ or SYC).

### Method

Each patient's age and sex were noted, as well as best corrected visual acuity, measured on a retroilluminated Light-house for the Blind (New York, NY, USA) distance visual acuity chart (using modified Early Treatment Diabetic Retinopathy charts 1, 2, and R) following the same protocol of refraction and visual acuity determination used in the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Study.<sup>2</sup>

At the first angiographic study 6–12 weeks after PDT, each patient was asked two questions by one of us (AB):

- (1) "Did you observe any luminous or coloured phenomenon after the session of verteporfin therapy and laser?"
- (2) "Did you experience visual hallucinations after the session?"

When visual symptoms were present, patients were asked to describe them, and to state the dominant colour, the time that elapsed from photocoagulation to symptom occurrence, and the course of the symptoms. The last question was then asked:

- (3) "Are you sure that these phenomena were not present before the treatment?"

On the basis of patients' replies to the three questions, they were classified into three groups: those without visual hallucinations (group 1), those with photopsias (group 2), and those with structured hallucinations (group 3). The groups were compared by the means of  $\chi^2$  test for categorical variables, by analysis of variance (ANOVA) and by Scheffe's test for continuous variables to establish whether age, sex, and/or visual acuity are risk factors for structured visual hallucinations.

**Table 1** Summary of cases

| Patients | Age | Sex | Treated eye | Initial VA           | Occurrence after PDT | Period, favourable circumstances   | Description of hallucination                 |
|----------|-----|-----|-------------|----------------------|----------------------|------------------------------------|--|
| 1        | 83  | M   | Right       | R 20/200<br>L 20/32  | 3 days               | once or twice a day                | white wheel                                  |
| 2        | 82  | F   | Right       | R 20/126<br>L 20/800 | 1 month              | variable                           | faces, miscellaneous objects such as parcels |
| 3        | 77  | F   | Left        | R 20/40<br>L 20/64   | 2 days               | when watching TV                   | alternating purple squares                   |
| 4        | 80  | F   | Left        | R 20/100<br>L 20/160 | 2 weeks              | variable, usually when watching TV | known and unknown faces                      |
| 5        | 88  | F   | Left        | R 20/80<br>L 20/320  | 2 or 3 days          | several times a day                | white shooting star with a circular movement |

PDT = photodynamic therapy.

## RESULTS

One hundred consecutive patients were included. They comprised 58 women (58%) and 42 men aged 50–95 years (mean 78.5). Eighty patients (80%) reported no visual hallucinations after PDT. Fifteen (15%) reported photopsias or flashing lights and five (5%) described structured complex visual hallucinations.

As stated in the Methods section, patients' replies to the three questions enabled three groups to be distinguished.

Group 1 comprised 80 patients, 47 women and 33 men, aged 50–86 years (mean 78.5). Their best corrected visual acuity ranged from 38 to 63 letters, when they were asked the three questions.

Group 2 comprised 15 patients, eight men and seven women, aged 68–84 years (mean 77.3). Their best corrected visual acuity ranged from 23 to 67 letters.

Group 3 comprised five patients, four women and one man, aged 77–88 years (mean 82). Their best corrected visual acuity ranged from 42 to 63 letters. Structured hallucinations varied greatly from one patient to another. Characteristics of members of group 3 are summarised in Table 1. In all patients, hallucinations were still present 3 months after treatment. All patients except case 3 denied having experienced similar phenomena before PDT. Case 3 thought he had experienced such hallucinations before PDT, but said they were more frequent and clearer than before treatment.

Between group comparisons by ANOVA and the  $\chi^2$  and Sheffe's tests to identify risk factors for structured visual hallucinations revealed no differences with regard to sex ( $p=0.406$ ), age ( $p=0.435$ ), or visual acuity ( $p=0.835$ ).

## DISCUSSION

We report here the occurrence of complex and structured visual hallucinations after PDT with verteporfin. To our knowledge, such hallucinations have not been previously reported, despite two large randomised clinical trials including patients with AMD,<sup>2,4</sup> one large randomised clinical trial involving patients with CNV caused by pathological myopia,<sup>5</sup> and several non-randomised studies of patients with CNV caused by other conditions.<sup>15,16</sup> Among the clinical trials in which patients experienced visual disturbances after PDT, these disorders were reported by 18% of verteporfin treated AMD patients, versus 12% of those given placebo, in the TAP study<sup>2</sup>; by 42% versus 30% of the corresponding groups in the Verteporfin in Photodynamic Therapy (VIP) Study of AMD patients with occult CNV<sup>4</sup>; and by myopic patients with CNV (21% in each group).<sup>5</sup> Visual disturbances consisted of abnormal vision, decreased vision, and visual field defects.

In the present study, the most curious finding was the description of complex and structured visual hallucinations by five patients (5%), corresponding to the CBS. In 1769, Charles Bonnet described complex visual hallucinations in his psychologically normal grandfather.<sup>17</sup> Different definitions

were given to the syndrome, depending on the presence or absence of ophthalmic problems<sup>9–13,18</sup> De Morsier, who named the syndrome, thought that ophthalmic disturbances were not necessary to define the syndrome which, according to him, consisted of visual hallucinations in elderly patients in full possession of their faculties without any delusions.<sup>18</sup> However, the syndrome has often been reported in patients with visual impairment due to visual deprivation.<sup>9,11,12</sup> In addition, a large prospective study indicated that common risk factors of CBS were age over 64 years and visual acuity in the better eye of 0.3 or less.<sup>12</sup>

There are few data concerning the prevalence of CBS, although most authors consider it to be underestimated.<sup>9,13</sup> Patients do not usually describe their hallucinations spontaneously, because they are afraid of being thought mentally ill. Psychiatric studies showed that CBS could be diagnosed in 1–2% of elderly patients referred for psychiatric inpatient care,<sup>9</sup> and among patients referred to a psychiatrist because of visual hallucinations.<sup>10</sup> CBS is more prevalent among visually impaired people: thus, it was diagnosed in 17 (25%) of 66 patients who became blind over a 1 year period,<sup>19</sup> and, recently, in the largest series reported, the prevalence of CBS was estimated at 11% in low vision patients, using very precise criteria: the presence of structured, complex, persistent, and repetitive visual hallucinations; full or partial retention of insight; absence of delusions; and absence of other kinds of hallucinations.<sup>12</sup> In another large study of a low vision population, CBS was found to be very common in the study population, as it was observed in 38% of patients.<sup>20</sup>

Although the association of CBS with AMD has been reported in small series,<sup>21</sup> and larger studies,<sup>6,12</sup> to our knowledge, CBS is not known as a possible complication of photodynamic therapy. Visual hallucinations have systematically been searched for in patients with CNV. Brown *et al* reported that unstructured hallucinations—that is, photopsias, were experienced by 59 of 100 patients, and that 12 patients also complained of structured visual hallucinations.<sup>6</sup> Most of the hallucinations reported were faces (42%), alternating squares (25%), flowers (25%), and fences (17%). The symptoms were found to be most common in older patients and patients with bilateral CNV. However, the hallucinations were reported before any treatment of CNV. In the present study, in contrast, all patients with structured visual hallucinations, except one, denied having experienced such phenomena before PDT. We cannot, however, rule out the possibility that patients denied having such symptoms because they did not want to be considered as chronic psychiatric cases.

The origin of visual hallucinations remains unclear. The causes suggested include irritative mechanisms caused by anatomical changes, which might generate photopsias and unstructured hallucinations, and release phenomena secondary to sensory deprivation that are more likely to cause structured visual hallucinations and the CBS.<sup>22</sup> The anatomical

changes observed after PDT might be involved in the occurrence of photopsias. However, the origin of complex visual hallucinations remains unclear. CBS was recently described as a frequent side effect of macular photocoagulation which occurred in 10 (16.6%) out of 60 patients,<sup>7</sup> and was also reported in two patients after surgical macular translocation.<sup>8</sup> In the former study, anatomical destruction of the fovea may have caused acute visual deprivation, a well known factor favouring structured hallucinations.<sup>23</sup> In the latter study, visual hallucinations occurred when the fovea was detached, and ceased after retinal reattachment and visual improvement.<sup>8</sup> In the present study, patients were not examined during the symptoms, and we were therefore unable to correlate these symptoms with a transient decrease in visual acuity. Our hypothesis is that an acute anatomical change of the macula—for example, because of fast resolution of the macular oedema, may be sufficient to trigger the occurrence of CBS in some patients. However, we were not able to find a common denominator for these patients.

Whatever their origin, the hallucinations appear to be a possible, by no means rare, side effect of PDT for CNV. The present results suggest the need to include the eventuality of visual hallucinations in the information given to all patients before PDT, and to conduct a systematic search for their occurrence after treatment, because patients will be relieved to know that they do not suffer from Alzheimer's disease or other psychopathology.

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