SCIENTIFIC REPORT

Seasonal variations of acute massive submacular haemorrhage associated with age-related macular degeneration

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Aims: To determine whether there is a seasonal variation in the onset of acute, massive submacular haemorrhage associated with age-related macular degeneration.

Methods: Sixty eyes of 59 patients diagnosed between April 1998 and March 2005, were studied retrospectively. For each patient, the month and season of onset of the submacular haemorrhage and the mean monthly ambient temperature in Nagoya were analysed. Any history of systemic hypertension was also recorded, and the seasonal variations were also investigated in hypertensive and non-hypertensive groups.

Results: The number of cases peaked in winter with a trough in summer, and this seasonal variation was significant (Roger's $R=12.03$, $p<0.01$). The monthly incidence was inversely correlated with the temperature (Spearman's rank correlation coefficient $r=0.89$, $p<0.01$). The seasonal variations were significant in the hypertensive group but not in the non-hypertensive group.

Conclusion: The considerable seasonal variations suggests that the mechanism for the haemorrhage is strongly correlated with the systemic blood pressure.

A seasonal variation has been often reported in the incidence and mortality of various systemic diseases. For instance, the incidence of onset of cerebrovascular and cardiovascular diseases is reported to have a peak in winter–spring and a trough in summer–autumn.^{1–5} This relationship is correlated with the ambient temperature. However, such seasonal variations have not been examined for ocular vascular diseases, although non-vascular ocular diseases have seasonal variations.

The mean number of sunshine hours is inversely related to the incidence of acute glaucoma,⁶ and intraocular pressure was reported to be higher in winter than in summer.⁷ One study reported that a considerable increase in the incidence of acute anterior uveitis was seen between August and December, and this increase was confined predominantly to HLA-B27-negative patients.⁸

Acute submacular haemorrhage occurs as a complication of neovascular age-related macular degeneration (AMD), but little is known about seasonal variations in the onset of acute massive submacular haemorrhage. We hypothesised that the onset of acute submacular haemorrhage associated with AMD has a seasonal variation similar to that for cerebrovascular or cardiovascular diseases. The general interest in this haemorrhage has increased recently, because massive submacular haemorrhage can occur after photodynamic therapy (PDT) for AMD,⁹ and visual outcome is not always good even with vitreoretinal surgical techniques using tissue plasminogen activator.^{10 11}

METHODS

The medical charts of 60 eyes of 59 consecutive patients (35 men and 24 women) with acute massive submacular haemorrhage associated with AMD and diagnosed at Nagoya University Hospital (Nagoya, Japan) from April 1998 to March 2005 were reviewed retrospectively. One case was bilateral. All patients were living in Nagoya city or its suburbs. Patients who had a submacular haemorrhage >3 disc diameter involving the fovea, and of sudden onset were studied. A diagnosis of AMD was made by slit-lamp biomicroscopy, colour fundus photography and fluorescein angiography. In all, 25 eyes of 25 patients underwent indocyanine green angiography and 28 eyes of 28 patients underwent optical coherence tomography.

For each patient, the month and season of onset, the mean ambient temperature of that month in Nagoya, and the patient's blood pressure were recorded. The mean monthly ambient temperature in Nagoya was obtained from the Japan Meteorological Agency, Tokyo, Japan. We defined March, April and May as spring; June, July and August as summer; September, October and November as autumn; and December, January and February as winter. We also divided the patients into two groups according to their systemic blood pressure, and investigated the seasonal variation in those classified as being hypertensive (systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90 mm Hg) and in those who were non-hypertensive.

Statistical analysis

Statistical analysis for cyclic trends was carried out using the method developed by Roger, which is sensitive to cyclic trends based on a cosine function.^{2 12} The correlation between the environmental temperature and monthly incidence was analysed using Spearman's rank correlation coefficient.

RESULTS

The monthly number of cases of acute massive submacular haemorrhage from January to December was 8, 6, 4, 4, 6, 2, 1, 3, 3, 6, 6 and 11 (fig 1). The monthly mean temperature at Nagoya is shown in fig 1. A significant seasonal variation in the monthly incidence of submacular haemorrhage associated with AMD was identified (Roger's $R=12.03$, $p<0.01$). A significant inverse correlation was found between the monthly incidence of acute-massive submacular haemorrhage and mean ambient temperature in Nagoya ($p<0.01$ and Spearman's rank correlation coefficient $r=0.89$; fig 2).

In total, 21 of the 59 patients (36%) were hypertensive, and considerable seasonal variation was identified in this group. Seasonal variation was not detected in the 36 patients who

Abbreviations: AMD, age-related macular degeneration; PDT, photodynamic therapy

were non-hypertensive (Roger's $R = 11.44$ and 3.90 , $p < 0.01$ and $p > 0.1$, respectively; fig 3).

DISCUSSION

Marked seasonal variation was found in the incidence of acute massive submacular haemorrhage associated with AMD. The variation was inversely correlated with the mean ambient temperature and was found in patients who were hypertensive, but not in patients who were non-hypertensive.

Cerebrovascular and cardiovascular diseases have been shown to have seasonal variations, and many studies have been published on the seasonality of these diseases. For example, considerable seasonal variations in the onset of primary intracerebral haemorrhage and cerebral infarction were found to peak in the winter, with a trough in the summer.²⁻³ Lower ambient temperatures (winter) were associated with an increased risk of hospitalisation for stroke and acute myocardial infarction in young women.⁴ All of these morbidities peaked in the winter, with a trough in the summer, as in our patients with acute submacular haemorrhage. The cause for these seasonal variations has been explained by changes in ambient temperatures^{1-5 13 14} and increases in fibrinogen concentrations.¹⁵

Blood pressure also has seasonal variations, peaking in January and February, with a trough in July and August.¹⁶ This variation is also correlated with the ambient temperature. In addition, cold weather has been shown to lead to greater fluctuations in blood pressure, especially among elderly people, obese people¹⁷ and smokers.¹⁸ These changes may be one of the reasons why the incidence of these diseases peaks in the winter.

The mechanism of how acute massive submacular haemorrhage develops has still not been determined. However, the coincidence of the cycle of submacular haemorrhage associated with AMD and that of systemic vascular diseases suggests that the same factors may be associated—namely, more fragile neovascular vessels that might rupture more often under higher blood pressure and greater fluctuations of that higher blood pressure. Because hypertension has long

Figure 1 (A) Monthly variation of acute massive subretinal haemorrhages (□) and mean ambient temperature in Nagoya city (●). (B) Seasonal variation in patients.

Figure 2 The relationship between mean ambient temperature and number of cases by month. The relationship is significantly correlated.

Figure 3 (A) Monthly variation of number of patients with (◇) and without (▲) hypertension. (B) Seasonal variation of patients with and without hypertension.

been suspected to be a risk factor for the incidence of advanced AMD,¹⁹ it may induce not only a progression of AMD but also the rupture of neovascular vessels. Further investigations are needed to determine the cause of the seasonality and mechanism of the development of acute submacular haemorrhage.

PDT is now one of the most commonly performed therapeutic procedures to treat wet AMD. However, acute massive submacular haemorrhages have been seen after PDT in a small number of patients, and have caused severe visual loss.⁹ Because acute massive submacular haemorrhage occurred much more often in winter than in summer in our patient series, more careful attention may be necessary after PDT in the winter.

In conclusion, a considerable seasonal variation of acute massive submacular haemorrhage associated with AMD was identified, and the monthly incidence was negatively correlated with the mean ambient temperature in Nagoya. Considerable seasonal variation was observed in patients with hypertension, but not in patients who were non-hypertensive. Further investigation is needed to identify the factors that affect the seasonal variation, and it may help to elucidate the mechanism of the acute onset of massive haemorrhage associated with AMD.

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