Cyclic variation in onset of central retinal vein occlusion

MICHAEL J LAVIN and BAL J DHILLON
From the Western Ophthalmic Hospital, Marylebone Road, London NW1

SUMMARY  We studied the seasonal incidence of onset of symptoms of central retinal vein occlusion (CRVO) in 105 patients over a 5-year period. Their onset showed a significant cyclic variation (p<0-01), being most frequent in the months September through to February. We believe this seasonal variation may in part reflect seasonal changes in haemostasis and retinal perfusion, though other unidentified factors play a significant role.

Although central retinal vein occlusion (CRVO) is a relatively common disorder, its aetiology remains unknown. It is often associated with endogenous disease such as atheroma, diabetes mellitus, and raised intraocular pressure, and exogenous factors are not known to influence its onset. Theories of origin include endothelial swelling, arterial hypoperfusion, and thrombotic venous occlusion. The debate on the primacy of arterial versus venous factors in the genesis of CRVO is not resolved. Since systemic arterial diseases such as peripheral arterial emboli, myocardial infarctions, and cerebrovascular accidents show a seasonal variation related to temperature, while systemic venous diseases do not, we studied the seasonal variation of CRVO in order to gain clues to its origin.

Patients and methods

Patients with a CRVO were identified from the fluorescein angiography index file at the Western Ophthalmic Hospital. Only consecutive new cases with dates of onset between September 1979 and the end of August 1984 were included. Patients’ notes were traced and the date of onset of symptoms was recorded, as were each patient’s age and sex. Patients were included only if a CRVO was shown on fluorescein angiography and an accurate date of the onset of symptoms was noted. Cases were classified as ischaemic or non-ischaemic on the basis of the fluorescein angiogram. The monthly incidence of CRVOs was charted and the results analysed.

The method of Edwards was used to test for the presence of cyclic variation.

Correspondence to Mr M Lavin, FRCS, Moorfields Eye Hospital, City Road, London EC1V 2PD.

Results

The frequency of onset of CRVO was much greater in the six months from September to February (72 cases) than in the subsequent six months from March to August (33 cases, Fig. 1). The distribution was bimodal, with peaks occurring in September and February. The annual variation was similar for both ischaemic and non-ischaemic CRVOs. There was no clustering by age or sex. The variation was present in all years.

By Edwards’s method the frequency of onset of CRVO shows significant cyclic variation (p<0-01). When the six-month period with the greatest frequency of cases (September to February) was compared with the six months March to August, a significant difference was found (χ²=14-48, p<0-001). A weak inverse correlation with the monthly temperature was noted (r=−0-48). A weak positive correlation with the monthly frequency of deaths from respiratory disease in England and Wales (1962 to 1964) was found (r=0-50). Correlations with
Cyclic variation in onset of central retinal vein occlusion

published figures of the seasonal variation in myocardial infarction\(^9\) (r=-0.23), peripheral arterial emboli\(^8\) (r=-0.23), and arterial blood pressure\(^11\) (r=0.25) were poor.

Discussion

The epidemiology of CRVO is characterised by a nocturnal onset and a peak frequency in the 7th decade of life, with less than 10% of patients under the age of 40 years.\(^7\) We also found a significant annual variation, suggesting that exogenous influences may be important. We are not aware of any previous reports of an annual variation in CRVO onset.

The bimodal peak suggests that different factors may account for the excesses seen in September and February. If the first peak is ignored, the variation in onset of CRVO is very similar to the variations in temperature for the period 1979 to 1984. This suggests that the February excess and summer paucity of cases of CRVO may be related to environmental temperature changes, though separate factors must explain the September peak.

A seasonal incidence of CRVO may be compatible with a thrombotic aetiology. Myocardial infarctions and cerebrovascular accidents are more frequent in winter than other seasons and show close correlations with temperature.\(^8\) Cold temperature is associated with a decrease in blood levels of antithrombin 3, with increased risk of thrombosis,\(^12\) and CRVO is a disease of the elderly, who have impaired thermoregulatory mechanisms.\(^13\) In addition exposure to cold increases both whole blood and plasma viscosity, the volume of plasma occupied by platelets, and the arterial blood pressure.\(^14\) It is likely that seasonal variations in blood pressure\(^11\) and haemostatic factors,\(^1\) perhaps induced by changes in core body temperature, are partly responsible for the variation in onset of CRVO found in this study. However, this would not explain the early peak seen in September.

Patients with CRVO are known to have a high incidence of associated systemic diseases, including chronic obstructive airways disease (COAD).\(^15\) COAD displays well recognised winter exacerbations, which are associated with increasing hypoxia. Hypoxia impairs red cell deformability and increases red cell viscosity,\(^16\) and this will alter blood flow properties. In addition hypoxia increases retinal vasodilatation, and in the presence of arterial insufficiency this may precipitate stasis, leading to vascular occlusion.

Endothelial swelling has been thought to play a part in the pathogenesis of CRVO,\(^7\) and together with the seasonal incidence found in this study it might be interpreted as evidence for an infectious aetiology. While a number of virus infections show a winter peak, a bimodal peak in September and February could not be identified in virological records (Public Health Laboratory, Colindale, personal communication, 1985). Although C-reactive protein levels (a non-specific indicator of inflammatory activity) are increased in CRVO patients as compared with controls,\(^17\) the elevation is very modest and not at the levels seen in inflammatory disease. Moreover, recent histopathological studies discount the role of inflammation in ischaemic CRVO, showing rather that thrombosis is the primary event, with an inflammatory cell infiltrate occurring secondarily in response to clot formation.\(^5\)

Raised intraocular pressure contributes to the development of a CRVO.\(^1\) We are not aware of any studies of seasonal variation of human intraocular pressure, though studies of the rabbit have shown small seasonal variations with peaks in summer and winter.\(^18\) Such small variations are unlikely to be relevant to the question of human CRVO.

The question must arise whether these results are an artefact. All our patients had presented directly to the Western Ophthalmic Hospital, and secondary referrals were not included. Consultant policy regarding fluorescein angiography has not changed significantly during the period studied. Attendances at the Casualty Department show a very small seasonal variation (with a summer peak), which does not account for our findings, particularly as patients presented at widely varying intervals after onset of CRVO. Data were collected in a randomised and unbiased fashion. When the results were plotted for sequential years the seasonal variation was seen with each successive graph.

However, certain possible sources of error do exist. This was a retrospective study, and patients were seen by a variety of doctors, which may have resulted in errors of dating onset, and many patients with CRVO were not included because the date of onset was not known. These factors are unlikely to explain our findings, since they would be expected to provide a constant error. Further, CRVO may often be asymptomatic, with symptoms supervening only when macular oedema or increasing ischaemia occurs. The variation we have recorded could therefore be a reflection of factors influencing visual function in patients with CRVO rather than onset of CRVO.

It is possible that our findings apply only to a specific subset of CRVO. In our study 43% of patients had severe, ischaemic CRVOS as compared with a general incidence of 22% of all CRVOS.\(^7\) The weighting in favour of the more severe forms of CRVO is not surprising, since this study required a
definite date of onset of symptoms and fluorescein angiography, which are features far more frequent in severe CRVOs. Although we found no difference in the seasonal incidence of CRVOs classified as ischaemic or non-ischaemic, it is possible that in some patients we have measured the onset of symptoms in longstanding, previously asymptomatic CRVOs.

While the cyclic trends in CRVO are similar to those in arterial diseases in having a relative paucity of summer cases, with an excess in the colder months, the bimodal incidence of CRVO is clearly different and correlated poorly with the actual incidence of arterial emboli, suggesting the influence of several factors.

To elucidate further the aetiological factors in CRVO, longitudinal studies need to be performed to document the history accurately and to identify blood rheological and clotting abnormalities. Such studies may allow the further characterisation of an at-risk population. Insight into the pathophysiology of CRVO could permit the design of specific therapy.

In conclusion, we have demonstrated a significant cyclic variation in the onset of CRVO, suggesting that exogenous factors may be important in its pathogenesis in addition to the well recognised association with endogenous disease. It is likely that part of this variation reflects temperature associated changes in haemostasis and retinal perfusion, though the early peak is not explained.

We thank Mr Ron Marsh for encouragement and access to records, and Sir Stanley Peart for helpful comments. We are grateful to Ms Karen Johnstone for the figure.

References

2 Klein BA. Occlusion of the central retinal vein: clinical import-


Accepted for publication 17 April 1986.