Introduction

During the last three decades 215 patients have been operated on in the neurosurgical department of the Leiden University Hospital, because of intracerebral hematomas. The etiology has been studied hematologically and roentgenologically before and after the intervention, and also by neuropathological examination of biopsies taken from the wall of hematomas during surgery.

After careful analysis 104 cases are left in which no specific pathological background could be established at the time of the treatment or thereafter. Such a group of so-called spontaneous hematomas is represented in the case material of any neurological-neurosurgical centres in the world, but it seems to be rather large in our case material in comparison with, for instance, the finding of Jellinger of about 15%.9

Within our group a considerable number of patients appeared to belong to some families from Katwijk, a small fisherman’s village at the North Sea coast near Leiden, with a total population nowadays of 16,577 inhabitants.12,13,15 From the start of the Leiden neurosurgical department in 1955, it was obvious that this subgroup of spontaneous intracerebral hemorrhages had to be distinguished as a special entity. Moreover its heredity was well known to the members of the respective families.

They were very much aware of it and when accompanying such a patient into the hospital they usually asked whether they themselves might also become a victim of this disease in the future. Verjaal had the same experience with some comparable cases from Scheveningen, another fisherman’s village at the border of the North Sea, near to the Hague.13 Outside Holland such familial cerebral hemorrhages are only described in the population of the northwestern area of Iceland.1,6-8

Our study has been restricted to 136 patients all belonging to three large families from Katwijk.16 Based on pathological, clinical and anamnestic data, the cases are classified in three groups: I) in 55 patients the cerebral hemorrhage was demonstrated by CT scan, by surgical exploration and/or by autopsy; II) in 22 patients the diagnosis of the cerebral hemorrhage was made probable by clinical neurological observation, and III) 59 other patients—not being hospitalized—were indicated as typical cases by family members and whenever possible confirmed by general practitioners.

Clinical Features

In our case material and also in Scheveningen, the hereditary intracerebral bleeding occurs mostly in the age-period of 45 to 65 years, preponderantly during the first half of the 6th decade of life.

In only two patients the vascular accident appeared at a younger age for the first time and in three others the hemorrhage occurred after the age of 65 years. The hemorrhage manifests itself rather suddenly like any other cerebrovascular accident. Usually progressive headache, vertigo and nausea, are followed by loss of consciousness and then by a coma. The clinical picture is completed in some hours. In a few cases it takes some days, however. In some patients a slight cerebrovascular accident may precede a definite stroke by 3 to 8 years. Usually such minor attacks are forgotten but will be remembered by the relatives when the patient is admitted to hospital. In a few cases the symptomatology may differ from the foregoing description. It consists of parietal, temporal and occipital hemorrhages without disturbed
consciousness, but with homonymous hemianopia, dysphasia and/or a slight hemiparesis only. Two patients with a temporal bleeding had a transient loss of memory and wandering around. In two other patients had signs and symptoms of a subarachnoid hemorrhage; two cases were initially diagnosed as a cranio-cerebral trauma, in one of whom a severe traffic accident had evidently been the consequence of his bleeding. In about 30 cases in Group I, progressive signs of intracranial hypertension indicated an expanding intracerebral hematoma which was surgically removed. During this procedure the walls of the hematoma was biopsied. Less progressive hemorrhages were treated conservatively. None of the patients had a hemorrhagic diathesis or another internal disease. Three patients were treated with anticoagulants but none of them had an excessive coagulation time. In three cases only a slight arterial hypertension existed before hospital admission, with diastolic pressure of 110 mmHg at a maximum. The blood pressure temporarily rose in cases of expanding hematomas due to intracranial hypertension (Cushing reflex). After evacuation of the hematoma it was reduced to normal values, however.

The prognosis of familial intracerebral hemorrhages is poor. Two thirds of the patients died after a severe cerebrovascular accident. Survivors have a high risk of recurrence after some time which may vary from three weeks to 14 years (average 4.5 years). A small number of the survivors suffered from — mostly focal — epilepsy and needed an anticonvulsant therapy, sometimes only temporarily. In other cases a presenile dementia developed.

Neuropathology

In 30 patients with hereditary cerebral hemorrhages autopsy was performed. Neuropathological study of the brain in all these cases revealed more or less identical features. Gross examination of coronal section of the brain showed one or more large, often slit-like, hemorrhages. In cases of more than one bleeding, the hemorrhage evidently occurred at different times. All hemorrhages occurred in the white matter, sometimes extending to the ventricular wall and often to the cortical surface. Hemorrhages occurred in the right as well as in the left hemisphere. The hemorrhage predominantly occurred in the temporal, parietal and occipital lobes or in their border areas, which is different from the hypertensive hemorrhages in the basal ganglia, in the brain stem or in the white matter of the cerebellum. Wedge-formed infarctions so often seen in arterial thrombosis or embolias are not seen in familial cases. Cerebral atrophy is not found more than expected from the age.

In the vicinity of the cerebral hemorrhages the arterial walls show sclerosis and hyalinization. Congo red staining, and examination with polarized light and with electronmicroscope reveal the presence of amyloid conglomerations. The microscopical picture consists of an extreme degree of congophilic angiopathy. Although amyloid angiopathy is also seen in normally aging brains and in Alzheimer’s dementia, it is much less prominent than in familial cerebral hemorrhage. In our cases senile plaques and Alzheimer’s fibrils are not or only scarcely seen. The amyloid arteriolosclerosis is predominantly located in the superficial layers of the cerebral parenchyma, and appears to be concentrated in the direct vicinity of hemorrhages and in infarctions but also in areas where such pathology is not existing. In addition, the small arteries in the covering arachnoid often have a tortuous course and show amyloid deposits in their thickened wall also. The amyloid angiopathy was also found in 28 of the 30 biopsies from the hematoma walls. Usually more than 10% of the cortical arterioles are affected. Some small clusters have also been seen in the cerebellar cortex but they have never been found in the basal ganglia and the brainstem. Careful examination has never revealed its presence outside the central nervous system, especially not in visceral organs. The amyloid deposits in the arteriolar walls will lead to a narrowing or even an obstruction of the vascular lumen with consequent infarction. Bleeding may follow the stiffness of the vascular wall:

Genetic Aspects

Three Katwijk families, could be traced back to the end of the 17th and the beginning of the 18th century. They developed intracerebral hemorrhages during the last three or four generations. They were classified into three groups. The sex ratio did not significantly differ. From the distribution of cases it must be concluded that an autosomal dominant mode of inheritance exists, which is also the case in the families from Scheveningen (i.e. the other affected Dutch population) and also those from Iceland. The interconnections with isolated smaller Katwijk families have still to be found, as is also the case for the small Scheveningen families traced back to the middle of the 19th century. Up to now no geneal interconnections with Icelandic families could be established.
Incidence

The incidence of cerebral hemorrhages in the respective families has been estimated in the completely known generations. A total number of 341 Dutch individuals could be selected; 68 of them suffered from the familial cerebral bleeding and were classified into Group I, 26 into Group II and 68 into Group III. According to these findings the incidence in the studied case material amounted to 47.5%.

Comment

It may be assumed that hereditary amyloid angiopathy of cortical and subcortical arterioles leads to familial cerebral hemorrhages. This pathology has never been found outside the central nervous system.

In only one case cerebral amyloid angiopathy existed without consequent cerebral hemorrhage(s). It was a 59-year-old man who died from urinary infection apparently before a cerebrovascular accident had occurred. His brain showed only some old micro-infarctions. Many brains of older patients who belonged to one of the three families and who did not die from cerebral hemorrhages were carefully examined once more on cerebrovascular pathology. All cases appeared to be negative in this respect. In literature, cortical amyloid angiopathy has been described in a few incidental cases of intracerebral hematomas, but no indication of familial occurrence existed whatsoever. As far as known, familial hereditary intracerebral hemorrhage due to amyloid angiopathy occurs only in Iceland and in two Dutch fisherman’s villages at the North Sea coast, all with an autosomal dominant pattern of heredity. This raises the question how it occurs in two exclusive locations around the North Sea and part of the Atlantic. Up to now no geneal relations could be established.

Apart from its close clinical and pathological resemblances, there exists however, a striking difference between the Icelandic and Dutch groups which has to be underlined now. In the Icelandic patients the cerebrovascular accidents occur in considerably younger patients i.e. between 20 and 40 years of age than in the Dutch ones. It cannot completely be excluded however, that climatological factors, different habits of nourishment or other environmental aspects, may be responsible for it.

Anyhow it seems reasonable for the moment to accept two varieties in the hereditary amyloid cortical arteriolosclerosis leading to familial cerebral bleedings in Iceland and in Holland, respectively. The amyloid in the brain and cerebral vessels is built up by pre-albumins. In general this may also be the case in other familiar amyloidosis in which it is localized in other organs, however. In the Icelandic cases of familial hemorrhages biochemical examination has revealed that the amyloid is composed of cystatin C (gamma trace) which is an alkaline microprotein built up by 120 amino acids. This is probably also the case in the Dutch material. According to Frangione et al. the constitution of this cystatin C is changed however, in the sense of a mutation. If this finding will be confirmed by further studies the last doubt about the hereditary character of this disease should be abolished. Further study also of the Dutch case material has to be continued.

Finally I should like to raise my usual question, i.e. whether comparable examples of this exclusive disease may be known to you, here in Japan.

References

4) Gilles C, Bracher JM, Khoubesserian F, Van Der Haeghen JJ: Cerebral amyloid angiopathy as a cause of multiple intracerebral hemorrhages. Neurology (NY) 34: 730–735, 1984

Neurol Med Chir (Tokyo) 27, July 1987


Address reprint requests to: Willem Luyendijk, M.D., Academic Hospital, P.O. Box 9600, 2300 RC Leiden, The Netherlands.