Graves' Disease and Subarachnoid Hemorrhage: A Possible Familial Association

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ABSTRACT: We report the occurrence of cerebral aneurysms and subarachnoid hemorrhage (SAH) in a family with Graves' disease (GD). Nine affected individuals across three generations have GD alone; three in the same generation have SAH without GD; and three others in the same sibship have both conditions. The familial association of GD and SAH has not been previously described. The occurrence of these disorders in individuals of the same family and their coexistence in the same individuals suggests a possible genetic determination for some cerebral aneurysms and may imply a genetic locus related to that of Graves' disease.

RESUME: Maladie de Graves et hémorragie sous-arachnoidienne: une association familiale possible. Nous rapportons des cas d’anévrismes cérébraux et d’hémorragies sous-arachnoïdiennes (HSA) dans une famille atteinte de la maladie de Graves (MG). Neuf individus répartis sur trois générations ont la MG seulement; trois dans la même génération ont HSA sans MG et trois autres dans la même fratrie ont les deux affections. L’association familiale de MG et de HSA n’a jamais été décrite antérieurement. La présence de ces affections chez des individus appartenant à la même famille et leur coexistence chez un même individu suggère la possibilité qu’un facteur génétique soit responsable de certains cas d’anévrismes cérébraux et peut impliquer un locus génétique voisin de celui de la maladie de Graves.

The pathogenesis of cerebral aneurysms is poorly understood. Hemodynamic, degenerative and genetic factors have been implicated. A genetic etiology for some cerebral aneurysms is suspected because aneurysms occur in identical twins,1,4 in families5 and in conditions with a well-established mode of inheritance such as Ehlers-Danlos syndrome type IV, Marfan's syndrome, pseudoxanthoma elasticum, and polycystic kidney disease.6 Despite these observations, a genetic basis for cerebral aneurysms remains unproven and, although 177 cases of familial intracranial aneurysms have been reported, a clear pattern of inheritance has not been established.5 We report the coexistence of cerebral aneurysms and subarachnoid hemorrhage (SAH) with Graves' disease (GD) in 3 siblings from a family with GD and discuss the possible genetic basis of this association.

Patients and Methods

A 43 year old woman with GD (III-23) was admitted to the Montreal Neurological Hospital because of SAH. Four of her siblings also had GD and two had sustained a SAH from a ruptured cerebral aneurysm. A sister (III-24) in whom both conditions also coexisted provided detailed information on all family members. Her information was confirmed, when possible, by hospital records and by reports from private physicians. The diagnosis of GD is inferred for individuals II-1, 3, 4 and III-18 for whom medical records are unavailable but who were reported by the informant to have thyromegaly and exophthalmos, and for individuals III-7 and 8 treated for hyperthyroidism but for whom further clinical and laboratory confirmation is unavailable. The diagnosis of SAH is inferred for individuals III-6, 14 and 18 who suddenly collapsed and died from no other obvious cause.

The family (Figure 1) is of Anglo-Saxon origin and comes from a remote village of 4500 people in the Gaspé peninsula of Quebec. It is constituted of 102 individuals, widely distributed in eastern and western Canada. Individuals I-2 and I-3 were first cousins. Individual I-1 died at the age of 79 of an unspecified cancer and individual I-2 died at the age of 65 of unknown causes. Individual II-1 died at the age of 79 of an unspecified cancer and individual I-2 died at the age of 65 of unknown causes. Individual II-2 died of carcinoma of the throat at the age of 75 and had no history of hyperthyroidism. Individual II-6a died at the age of 56 of unspecified cancer. Individual II-6b was diabetic and hypertensive and died at the age of 81 of unknown causes.

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causes. Individuals in generation III are aged 40 to 60 years. The oldest individual in generation IV is 35 years. All individuals in generation V are younger than 20 years.

Involved individuals are gathered in three groups: Group A consists of 9 individuals with GD but without SAH; Group B consists of 3 individuals with suspected or confirmed SAH but without GD; and Group C consists of 3 individuals with GD and suspected or confirmed SAH.

Group A

Cases II-1, 3, 4 are three females who suffered from thyromegaly and exophthalmos. Individuals II-1 and II-4 died of unknown causes after a protracted illness in their seventh and sixth decades respectively. Individual II-3 died at age 74 of breast cancer. Autopsies were not performed.

III-7 is a male who has had a thyroidectomy for hyperthyroidism, and III-8 is a female who has also been treated for hyperthyroidism. III-17 is a female who suffered from thyromegaly and bilateral exophthalmus. She was treated with radioactive iodine and is presently on thyroid replacement therapy. III-21 is a female who was well until the age of 36 when she developed thyrotoxicosis and thyromegaly, and unilateral proptosis, lidlag and lid retraction, leading to the diagnosis of GD. Her thyroid indices and thyroid microsomal and thyroglobulin antibody levels were elevated and $^{131}$I scanning demonstrated diffuse uptake. She was treated with radioactive iodine and has remained euthyroid on thyroid replacement therapy.

IV-21 is a female whose father had thyromegaly and died suddenly at age 30. She presented to hospital at age 20 with nervousness, tremor, thyromegaly, unilateral exophthalmaus with widened palpebral fissure and lidlag, leading to the diagnosis of GD. Thyroid indices and microsomal antibody levels were elevated, thyrotropin levels were decreased and $^{131}$I thyroid uptake. She was treated with radioactive iodine and requires thyroid replacement therapy.

Group B

III-6 is a male who had no evidence of thyroid disease although a brother and sister both were treated for hyperthyroidism. He was well until the age of 30 when he suddenly collapsed while attending to his usual activities and rapidly died. Autopsy was not performed. III-14 is a female who had no evidence of thyroid disease although her mother had thyromegaly and exophthalmos. She was well until the age of 34 when she suddenly collapsed and died while washing dishes. Autopsy was not performed.

III-25 is a male who had 2 sisters with GD and documented SAH and 3 other siblings with GD, one of whom died of suspected SAH. He had a history of rheumatic heart disease, mitral stenosis, and hypertension. At the age of 49 he had the sudden onset of headache, vomiting, drowsiness, nuchal rigidity, a partial right third nerve palsy and weakness of the left arm. Xanthochromic cerebrospinal fluid (CSF) was obtained by lumbar puncture (LP) and cerebral angiography demonstrated a 10 mm x 4 mm aneurysm of the anterior communicating artery which was successfully clipped. Postoperatively he developed hydrocephalus, treated with ventriculo-peritoneal shunting, and generalized seizures well controlled with medication. He suddenly collapsed and died one year after surgery. Autopsy was not performed.

Group C

III-18 is a male who had uninvestigated and untreated thyromegaly but was otherwise well. He had 2 sisters with confirmed GD and SAH, 2 other sisters with GD, and a brother with confirmed SAH. He collapsed and died suddenly at the age of 30 while refueling his tractor. Autopsy was not performed.

III-23 is a normotensive female who has a history of suicide attempts and of non-compliance with psychiatric care. At the age of 39 she developed thyrotoxicosis, thyromegaly, unilateral proptosis, lidlag and lid retraction leading to the diagnosis of GD. The whole thyroid gland was enlarged and there was a palpable node in the right lobe. Thyroid indices and thyroid microsomal antibody levels were elevated and $^{131}$I thyroid uptake were found.

Figure 1 — Familial pedigree: 12 individuals have suspected or confirmed Graves' disease (II-1,-3,-4; III-7,-8,-17,-18,-21,-23,-24; IV-21,-22); six have suspected or confirmed subarachnoid hemorrhage (III-6,-14,-18,-23,-24,-25), and three (III-18,-23,-24) have both conditions.
scanning demonstrated diffuse uptake with focal accentuation in the right upper lobe. She was treated with Propylthiouracil and Propranolol and was euthyroid when last seen by her endocrinologist in January, 1985. A few months later she developed sudden severe occipital headache with nuchal rigidity, and xanthochromic CSF was obtained by LP. Computed tomography scanning and four vessel cerebral angiography were normal. She recovered from the SAH, was discharged from hospital in good condition, and remains well.

III-24 is a normotensive female who presented to hospital at the age of 21 with excessive sweating, bilateral exophthalmos, and thyromegaly leading to the diagnosis of GD. She underwent subtotal thyroidectomy and did not require thyroid replacement. She again presented to hospital at age 38 after developing a sudden severe headache and nuchal rigidity. Lumbar puncture produced xanthochromic CSF and cerebral angiography demonstrated a 4 mm x 5 mm aneurysm at the origin of the left posterior communicating artery which was successfully clipped. She remains well 4 years later.

**DISCUSSION**

The familial coexistence of GD and SAH has not been previously reported. Graves' disease has a 0.3 - 2/100,000 per year incidence with a peak distribution in the third and fourth decades, a seven to tenfold female preponderance, and is often associated with HLA loci DR3, DW3 and DW12. Although GD is often familial a co-inherited HLA locus has not been identified for the familial form. We believe that our patients suffered from GD and not from another form of thyroid disease. Hyperthyroidism was confirmed in all patients whose laboratory investigations were available for study and all of these also had ophthalmopathy supporting the diagnosis of GD. The presence of elevated microsomal antibodies in some of the patients is not incompatible with this diagnosis. There is little doubt that the other patients who sought medical attention also suffered from hyperthyroidism because they were treated by thyroidectomy and with radioactive iodine. Many of these patients also had ophthalmopathy, supporting the diagnosis of GD. Finally, in a few patients the diagnosis of GD is inferred from the history of a goiter with exophthalmos. Other causes of goiter are less likely because they are not usually associated with ophthalmopathy. Several investigators have found an increased incidence of GD in relatives of patients with GD or toxic nodular goiter, and both autosomal dominant and recessive modes of inheritance have been suggested. If we assume that individuals I-1 or 2, II-2, II-6a and III-14 were carriers of GD because many of their children were affected, then the inheritance of GD in this family would be autosomal dominant. The incidence of GD, however, may be falsely low because of subclinical hyperthyroidism, incomplete follow-up and failure of many individuals to reach the age of manifestation of the disease.

Subarachnoid hemorrhage from cerebral aneurysms has an incidence, in North America, of 11/100,000 with a peak distribution in the sixth decade and, like GD, is more common in females. A possible genetic determination for some cerebral aneurysms is suspected because they occur in identical twins, in families and with some inherited disorders such as Ehlers-Danlos syndrome type IV, Marfan's syndrome, pseudo-xanthoma elasticum and polycystic kidney disease. One hundred and seventy-seven patients from 74 families harboring 243 cerebral aneurysms have been reported. Analysis of these cases fails to reveal a clear pattern of inheritance of familial cerebral aneurysms. Autosomal dominant and multifactorial transmission have been postulated but neither mechanism has been proven, and no co-inherited HLA locus has been reported with familial or sporadic aneurysms. The pattern of inheritance of aneurysms in our family is not obvious. It is possible that a coexisting familial connective tissue disorder produced sudden death in individuals III-6, 14 and 18, from myocardial infarction, cardiac arrhythmia, dissection or rupture of a great vessel or from other causes of sudden death associated with a collagen vascular disease. Examination of individuals III-23, 24 and 25 who had confirmed SAH, and of other individuals seen by a physician, did not, however, suggest the presence of a coexistent collagen vascular disorder in our family. It is unlikely, therefore, that individuals III-6, 14 and 18 had such a disorder and, in the absence of another obvious cause of sudden death, SAH is inferred. Individual III-23 had proven SAH, the cause of which could not be determined despite adequate angiography. This is the case in approximately 20% of patients with proven SAH. In these cases it is felt that SAH results from a vascular anomaly that is either beyond the resolution of angiography or that is destroyed at the time of rupture.

There are three possible explanations for the coexistence of GD and SAH in the same individuals or in individuals from the same family. First, the two disorders may be causally related. The hyperdynamic conditions associated with thyrotoxicosis could conceivably predispose to the formation of cerebral aneurysms or contribute to their rupture. This is unlikely because SAH is not usually associated with GD. The occurrence of documented SAH in 3 siblings, two from a proven cerebral aneurysm, does not necessarily mean that there is a familial determinant for cerebral aneurysms in our family. The second possibility, therefore, is that the occurrence of cerebral aneurysms and SAH in our family is sporadic and the association with familial GD is coincidental. A familial determination for cerebral aneurysms could be proven if the siblings or offspring of cases III-23-25 were studied for the presence of cerebral aneurysms. This would necessitate cerebral angiography with its associated risks and it is unclear whether this would be in the best interest of the individuals involved. Other radiological means of documenting the presence of a cerebral aneurysm have too high a false negative rate to be useful. The third possibility is that the two disorders are genetically determined and transmitted on separate or linked genes. In the former case the association of familial GD and familial SAH would be coincidental, both genes being inherited separately and independently. In the latter case the two genes would be co-inherited, indicating that the putative genetic locus for cerebral aneurysms is related to that of GD. Our data do not confirm or disprove either of these hypotheses. It could be argued that independent inheritance of GD and aneurysms is more likely because only a few individuals have both conditions. However, it is also possible that some individuals with GD harbored asymptomatic, therefore, undiagnosed cerebral aneurysms. It is well known that all cerebral aneurysms do not rupture in life and that they are often found incidentally at autopsies of patients who died of other causes. For the reasons already brought forward it is probably not justified to perform cerebral angiography in individuals with GD in our family although the demonstration of an aneurysm in individuals III 7, 8, 17 and 21 and IV 21, 22 would be critical observations.
The molecular basis for the inheritance of cerebral aneurysms remains unknown. Genetic linkage studies and HLA typing of members of families with familial aneurysms as is presently being performed in our laboratory, may shed some light on the genetics of cerebral aneurysms.

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