Summary of the Proceedings of the First International Workshop on CADASIL
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The acronym CADASIL for "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy" was recently suggested for the disease formerly called "hereditary multi-infarct dementia" by Sourander in 1977. This condition is characterized clinically by recurrent subcortical ischemic strokes starting in mid-adulthood and sometimes leading to pseudobulbar palsy and dementia. Other symptoms include migrainelike attacks of headache and psychiatric symptoms. Magnetic resonance imaging (MRI) of the brain is always abnormal and shows relatively consistent signs of small, deep infarcts and leukoencephalopathy. Pathology likewise shows numerous small, deep infarcts with diffuse myelin loss and pallor of the hemispheric white matter. The underlying lesion is a nonatherosclerotic nonamyloid angiopathy affecting mainly the small penetrating arteries of the subcortical white matter and basal ganglia. Genetic linkage analysis performed in two unrelated French families recently assigned the disease locus to chromosome 19q12.

Eight unrelated European families have thus far been reported that share similar clinical, neuroradiological, and pathological features. All physicians involved in the study of these eight families were invited to take part in the First International Workshop on CADASIL, which was also attended by a number of neurologists, psychiatrists, neuroradiologists, and neuropathologists presently dealing with nonreported affected families. The aim of the workshop was twofold: first, to establish a kind of "state of the art" of CADASIL, and second, to form the basis of a European study group for this condition.

First Session: Clinical Presentation of Affected Families

M.G. Bousser (Paris, France) summarized the clinical findings of one already-reported family. Among 57 living members analyzed, 11 (6 men, 5 women) had suffered recurrent subcortical ischemic events, starting at a mean age of 43.3 (range, 28 to 60) years. Eight of them had recurrent strokes, 2 had only transient ischemic attacks (TIAs), and 1 had both. Three later developed pseudobulbar palsy and subcortical dementia. Other symptoms included migrainelike attacks of headache, epilepsy, manic-depressive syndrome, and sensorineural hearing loss. An important negative finding was the absence or rarity of vascular risk factors. All patients had an abnormal brain MRI, with signs of small, deep infarcts and leukoencephalopathy. The white matter abnormality was also present in 8 totally asymptomatic subjects, each of them with an affected parent. It was the study of this pedigree that first allowed the mapping of CADASIL to chromosome 19, later confirmed in a second family.

P. Davous (Argenteuil, France) suggested that the two cases described by Van Bogaert in 1955 as "Binswanger's disease with a rapid course in 2 sisters" were possibly affected by CADASIL, thus giving Van Bogaert the credit of the first description. He also summarized a published pedigree in which four members developed, between 36 and 54 years of age, a subcortical dementia with focal neurological signs suggestive of stroke. Brain computed tomographic (CT) scan showed evidence of small, deep infaracts and leukoencephalopathy, which were confirmed at autopsy. In closing, Dr Davous mentioned a very large pedigree currently under study. In this pedigree, one patient presented with progressive onset of subcortical dementia in the absence of stroke history.

Sirocchi and M. Ragno (Ascoli Picceno, Italy) presented a large pedigree and gave details about three patients. The first had recurrent ischemic strokes starting at the age of 52 years that led to pseudobulbar palsy and dementia. The second patient suffered severe depression at the age of 50 years, a stroke at age 52, and later became demented. The third patient presented with a progressive subcortical dementia without focal deficits. The MRI findings were remarkably similar to those of other families.

M. Verin (Rennes, France) presented a four-generation pedigree with 12 clinically affected subjects and 3 subjects with abnormal MRI findings in the absence of symptoms. Although neuroimaging findings were similar to those of other families, the clinical presentation was somewhat different. It was remarkable for the frequency of attacks of migrainelike headache (10 of 12) and of psychiatric symptoms (7 of 12), depression being particularly frequent. There was also the usual history
of recurrent strokes (7 of 12), TIA (10 of 12), and subcortical dementia (7 of 12).

P. Scheltens (Amsterdam, The Netherlands) gave a brief presentation of two families he is currently studying in which several members have suffered recurrent strokes or subcortical dementia.

P. LeBars (Lille, France) described three cases of subcortical dementia (one progressive and two with a history of strokes) with a similar MRI pattern of small, deep infarcts and leukoencephalopathy, in the absence of hypertension. He wondered whether these cases (and others of Binswanger's disease without hypertension) could be sporadic forms of CADASIL. Interestingly, it was discovered that one patient who had not heard from her family for more than 18 years was a member of a large pedigree currently under study by the Paris group.

P. Burkhard (Geneva, Switzerland) showed a six-generation pedigree and described six affected subjects. They all were between 38 and 59 years of age when they exhibited neurological or psychiatric disturbances with recurrent focal deficits suggestive of ischemic symptoms. MRI showed small, deep infarcts and leukoencephalopathy. This family was also remarkable for the presence of polycystic renal disease with frequent hypertension. At present, it is unknown whether these features are associated diseases or part of CADASIL. They have not been observed in the other reported families.

R. Niemeyer (Hamburg, Germany) presented the case reports of two brothers from a family with a history of autosomal dominant recurrent strokes. One had a stroke, continued having pseudobulbar palsy, and committed suicide 2 years later. The other has had several ischemic episodes without dementia. Both were free of vascular risk factors, and both had MRI signs of small, deep infarcts and leukoencephalopathy.

G. Chazot (Lyon, France) discussed the case he previously published of one young patient who died at age 44 years after recurrent subcortical strokes and dementia.11

H. Chabriat (Paris, France) presented clinical and MRI data on 115 subjects from nine families (including four families already mentioned by previous speakers). Fifty-four subjects were affected on the basis of cerebral MRI, including 23 asymptomatic individuals (mean age, 35.4±9.7; range, 18 to 59 years), and 31 clinically affected individuals (mean age, 51±10.7; range, 29 to 72 years). The mean age at onset of clinical symptoms was 46.9±10 (range, 29 to 74) years. The main signs were recurrent subcortical ischemic strokes or TIA (89%), subcortical dementia (56%), mood or behavioral disturbances (manic episodes, depression, suicides, or suicide attempts) (22%), and seizures (7%). Subcortical dementia usually had a stepwise course with a history of recurrent strokes (80%), but it was progressive without focal deficits in 20%. Mean age at death, calculated in 19 subjects, was 58.7±10.1 (range, 42 to 77) years.

Many points were raised in the discussion. The first was the relationship between CADASIL and Binswanger's disease. Clearly, these two conditions have the same main clinical and radiological features except for the presence of hypertension in Binswanger's disease. It was felt that Binswanger's disease was a syndrome rather than an entity and CADASIL was one possible cause of this syndrome. The second point of discussion dealt with the frequency of headache similar to migraine in some of these families. It was thought that more attention should be paid to this symptom and further studies were needed using structured interview of all family members, including spouses and husbands of subjects affected with CADASIL. A third point seemed of great interest: the frequency of psychiatric disturbances such as atypical depressive or manic episodes that can be inaugural. Here again, it was felt that there was a great need of further psychiatric studies.

In most cases the hereditary nature of this condition was not immediately obvious, and its demonstration required systematic and extensive familial investigations. This point raises ethical questions that were also discussed, and the decision was made to organize a special ethical working group for CADASIL.

Second Session: Neuroimaging

P. Scheltens (Amsterdam, The Netherlands) summarized his work on white matter abnormalities shown on MRI in Alzheimer's disease. He showed that patients with Alzheimer's disease had more severe abnormalities of the white matter than age-matched control subjects.12 E.A. Cabanis and M.T. Iba-Zizen (Paris, France) presented data on nine CADASIL families studied with MRI (T1 and T2 corresponding images). Two main types of abnormalities were observed: first, small, deep, well-delineated areas of abnormal signal (decreased on T1-weighted and increased on T2-weighted imaging) highly suggestive of small infarcts; second, areas of hypersignal (on T2-weighted imaging) in the white matter of cerebral hemispheres. These areas were more or less extensive and seemed to spare the U fibers. They insisted on the absence of cortical lesions, on the relative symmetry of the white matter changes, and on their preponderance in the anterotemporal regions and in the external capsule. They suggested the hypothesis of a pattern of evolution in six stages: 1, normal; 2, isolated Virchow-Robin spaces dilatation; 3, symmetric, nodular, isolated areas of increased signal; 4, larger areas of increased signal in the external capsule and in the white matter of temporal lobes; 5, bihemispheric confluent areas of increased white matter signal; and 6, cerebellar and brain stem involvement. Dr Cabanis insisted on the probably crucial significance of the white matter disorder that was present not only in patients with clinical symptoms but also in a number of asymptomatic subjects. He also stressed the point that MRI was used to define the status of patients (affected or nonaffected) for the genetic linkage analysis.

Y. Roland (Rennes, France) described a large pedigree from Brittany. Seven subjects presented with abnormal MRI results; all had changes suggestive of small infarcts and a widespread white matter disorder. Again, these lesions were purely subcortical, affecting the basal ganglia and periventricular white matter (7 of 7) and also the brain stem (4 of 7) and cerebellum (2 of 7). All other participants described the same patterns of MRI lesions, which seem to be relatively similar in all families.

Cerebral angiography was performed in at least one affected member of all studied families. It was essentially normal except in the family from Switzerland (P. Burkhard), with dolicho-arteries, and in one of the French families (P. Davous), with an angiographic
aspect suggestive of fibromuscular dysplasia. These abnormalities have not been observed in other families. It was felt that they most likely were associated conditions.

Third Session: Genetics

E. Tournier-Lasserve reported the chromosomal genetic mapping of CADASIL on chromosome 19q12. Genetic linkage analysis was conducted on two unrelated French pedigrees by using highly polymorphic microsatellite markers from Génethon (France). The disease status for linkage analysis was established on cerebral MRI data. MRI phenotype penetrance was considered complete above 35 years of age. Several candidate genes coding for various components of the arterial wall, elastin, fibrillins, and collagen genes as well as the APP gene were first excluded. The ensuing sequential study of the whole genome assigned the most likely location for the CADASIL gene on chromosome 19, within the interval bracketed by D19S221 and D19S222 markers, without evidence of genetic heterogeneity.

J. Melki presented her experience on positional cloning of the recessive infantile form of spinal amyotrophy, emphasizing the need for numerous homogenous and informative families to reduce as much as possible the chromosomal interval containing the gene of interest.

M. Lathrop reported his recent data on the mapping of susceptibility genes in hypertensive rats and his approaches to identify genes implicated in human hypertension. Methodological problems encountered during the investigation of human polygenic diseases were raised.

Fourth Session: Pathology

Y. Olsson (Uppsala, Sweden) gave details about the pathological data, particularly the microvascular changes observed in four subjects from the first Swedish pedigree described by Sourander and Walinder in 1977. One patient died of cerebral hemorrhage. All presented with marked white matter atrophy, multiple small cystic infarcts, and lacunae involving the central gray and white matter and the pons. Small leptomeningeal and intracerebral arteries showed thickening of the wall with marked collagen deposits, degeneration of smooth muscle cells of the media, and obliteration of the lumen. Amyloid staining was negative. Regions with signs of vasogenic edema were present. Reactive astrocytes with endothelin-1-like immune reactivity in the cytoplasm were seen in some regions. Dr Olsson suggested that vasoactive substances such as endothelin 1 might play a role in the disease process by causing vasoconstriction.

P. Sourander (Uppsala, Sweden) discussed another familial condition observed in Finland and Japan, “polycystic osteodysplasia combined with sclerosis and leukoencephalopathy,” which could be interesting to investigate by genetic studies.

G.P. Pizzolato (Geneva, Switzerland) described results of brain biopsies obtained in two deceased patients from the family studied by Burkhard. In both he observed a diffuse demyelination associated with basal ganglia and white matter infarcts. A nonamyloid eosinophilic deposit was observed in the thickened arterial wall of the corresponding small arteries.

M. Baudrimont (Paris, France) reported the pathological findings in one subject from the first French pedigree. A recent capsulolenticular hematoma, multiple small deep infarcts, and a diffuse pallor of the hemispheric white matter sparing the U fibers were observed. The major underlying lesion was a widespread vasculopathy of the white matter, basal ganglia, and leptomeningeal arteries. The arterial nonamyloid cosinophilic deposit in the media with reduplication of the internal elastic lamella was different from arteriosclerotic and amyloid angiopathies. Electron microscopic examination showed within the arterial media an electron-dense, granular material at a distance from the internal elastic lamellae and in close relation to myocytes.

C. Fallet-Bianco (Paris, France) reported data on one subject belonging to the family described by Davous. An arteriopathic leukoencephalopathy with myelin loss and pallor of the white matter was again found. The underlying lesion was a nonarteriosclerotic, nonamyloid arteriopathy with severe thickening of the internal lamina and presence of degradation products of elastic fibers.

Very similar lesions associated with typical Alzheimer’s changes were presented by F. Gray (Creteil, France) in a Canadian patient whose parents both had dementia. The father as well as several brothers and sisters of the patient were reported as being affected by CADASIL. Interestingly, the mother had an Alzheimer’s-type dementia, raising the possibility that the patient had inherited both the CADASIL gene and a susceptibility gene for Alzheimer’s disease.

H.J. Colmant (Hamburg, Germany) described two remarkably large families, one with clinical and pathological data similar to CADASIL, the other with subcortical encephalopathy of the Binswanger type associated with early disc herniation as reported in some Japanese cases. The clinicopathological pattern of these Japanese cases is similar to that of CADASIL, but of the four subjects described, two had no family history and two were parents belonging to a family with a high degree of consanguinity. Dr Colmant insisted that the small-artery disease of CADASIL could also affect the spinal cord and other organs. He suggested that myocardial infarction in one of his cases might have been due to this arterial disease.

Conclusion

This first workshop on CADASIL proved extremely fruitful in that it greatly increased our knowledge of this condition. It first showed that the disease is not rare and that its prevalence has probably been underestimated. Taking into account all the families known to the participants, 25 white families have presently been identified in Europe and another possible one in Canada. Neurologists from other parts of the world who deal with similar families and who would like to share their experience with the present group are most welcome. It was confirmed during the meeting that the main clinical phenotype was that of stroke subtype infarcts leading to pseudobulbar palsy and vascular dementia, but the existence of other phenotypes was clearly shown: progressive dementia, depressive or manic epi-
sodes, and migraine-like headache. The meeting confirmed the crucial diagnostic importance of MRI, both for patients in whom it shows small subcortical infarcts and leukoencephalopathy and for asymptomatic subjects who occasionally have the same white matter disorder. As far as pathology is concerned, the presence in all these families of a remarkably similar small-artery disease resulting in small, deep infarcts, and leukoencephalopathy was confirmed. White matter penetrating arteries are constantly affected, but there seem to be important differences in the distribution of the arterial changes: only or mainly in the brain in some families and more diffuse in others. From the genetic point of view, the locus assignment was considered a major advance because, first, it will now allow the recruitment of homogeneous families, which is crucial for a better understanding of the condition; second, it provides a tool for the division of such fields as small, deep infarcts, vascular leukoencephalopathy, vascular dementia, and Binswanger’s disease; and third, it represents the first step toward the identification of the defective gene.

Although our knowledge of CADASIL has increased, a host of questions remain unanswered: What is its prevalence? Are there other phenotypes? What is the relationship between migraine and CADASIL, particularly in view of the fact that familial hemiplegic migraine also maps on chromosome 19?16 Is the leukoencephalopathy always the first manifestation of the disease preceding the onset of clinical signs? Is the leukoencephalopathy purely ischemic in origin? What is the pathophysiology of small infarcts? Why is the cortex spared? What is the nature of the granular deposit in the arterial wall? What could be the best therapeutic approaches?

Participants in the workshop have agreed to increase their collaborative work and to set up studies addressing some of these issues; it is hoped that new findings could be presented at a second CADASIL meeting in 1994.

References


Key Words • cerebral ischemia • dementia • hereditary diseases • leukoencephalopathy
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