Cerebrovascular Arteriopathy (Arteriosclerosis) and Ischemic Childhood Stroke

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SUMMARY The aim of this report is to describe the intracranial cerebrovascular abnormalities and clinical status of 8 children who had familial lipoprotein disorders and evidence of thromboembolic cerebrovascular disease. Six of the 8 children had low levels of plasma high density lipoprotein cholesterol, two had high triglyceride levels, and all came from kindreds characterized by familial lipoprotein abnormalities and premature cardio- and/or cerebrovascular atherosclerosis. Vascular occlusion, irregularities of the arterial lumen, beading, tortuosity, and evidence of collateralization were consistently noted. We speculate that cerebrovascular arteriosclerosis in pediatric ischemic stroke victims who have familial lipoprotein abnormalities may be related to lipoprotein-mediated endothelial damage and thrombosis formation, or to the failure to restore endothelial cells' integrity following damage. The apparent association of lipoproteins and strokes in children and their families merits further exploration, particularly when assessing cerebral angiograms in pediatric ischemic stroke victims. In children with unexplained ischemic cerebrovascular accidents, the diagnostic possibility of occlusive arteriosclerosis with thrombosis must be entertained.

CEREBROVASCULAR DISEASE IN CHILDHOOD can generally be classified as ischemic or hemorrhagic; 55% of cases at the Mayo Clinic (38 of 69) were ischemic, while 45% were hemorrhagic.1 Of the 38 cases of ischemic stroke, 34% (13 of 38) had no identified etiology.

In a recent retrospective study of unexplained ischemic cerebrovascular accidents (CVAs) at the Children's Hospital Medical Center, Cincinnati, Ohio, eleven children with unexplained ischemic CVAs were found over a 14-year period.2,3 Ten of the eleven children and all eleven kindreds had abnormal lipids or lipoproteins, predominantly low levels of high density lipoprotein cholesterol (C-HDL), and/or high levels of triglyceride. In all eleven kindreds, pervasive familial lipoprotein abnormalities were documented. In nine of the eleven kindreds, adult relatives of the pediatric stroke probands had sustained premature myocardial infarction and/or stroke.2,3 In these eleven kindreds, we speculated that familial lipoprotein abnormalities involving low levels of C-HDL and/or high triglyceride may have caused occlusive cerebrovascular arteriosclerosis, and thus may have predisposed the eleven children to non-hemorrhagic cerebrovascular strokes.2,3

Since the concept2,3 of cerebrovascular arteriosclerosis associated with familial lipoproteinemias may be new to pediatric neurologists and radiologists, the specific aim of this report is to review and describe the radiographic arterial abnormalities and clinical status in 8 children who have familial lipid disorders and evidence of thrombotic cerebrovascular disease.

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Materials and Methods

Study Population

Medical records of children, ages 1 to 17 years, with clinical and laboratory evidence of a non-hemorrhagic cerebrovascular accident, were reviewed for the past 14 years. Excluded were children who demonstrated preexisting or predisposing risk factors for CVA, including uncontrolled hypertension, collagen vascular disease, diabetes mellitus, congenital heart disease, cardiac valvular disease, septic emboli, trauma, leukemia, clotting abnormalities, and polycythemia. Migraine patients were also specifically excluded, and family history of migraine in the probands' first-degree relatives was absent. We also excluded children with the syndrome of acute infantile hemiplegia. Mitral value prolapse was excluded by echocardiography. After such exclusions, eleven cases of "unexplained" ischemic stroke were found,2,3 of whom seven (subjects 1–7, table) had cerebral angiograms. Prior to their acute strokes, they had been healthy and entirely asymptomatic, and by selection, none had known conditions which would have predisposed them to acute stroke. An additional subject (#8, table), a 13-year old girl, has been studied prospectively. Of the eight children, all were white, five were boys, and three were girls. Their ages at onset of acute stroke ranged from 19 months to 13 years, as shown in the table.

There was no selection bias (by lipoprotein abnormalities) for the 4 (of 12) pediatric stroke probands in whom angiograms were not done; these 4 probands included 2 with high density lipoprotein cholesterol ≤ the age-sex-race-specific 5th percentile, one with triglyceride > the 90th percentile, and one with low density lipoprotein cholesterol > the 90th percentile.2,3

Lipid and Lipoprotein Determinations

To avoid any metabolic impact of the acute stroke on plasma lipids and lipoproteins, fasting blood for lipoprotein quantitation was obtained at least six
months after the acute stroke event in the original seven children, with the children and their relatives fasting for twelve hours, and on their habitual ad libitum diet.2 3 In subject #8, fasting blood was obtained two months after her stroke. Fasting plasma cholesterol, high and low density lipoprotein cholesterol (C-HDL, C-LDL) were quantitated following the Lipid Research Clinic’s Laboratory Methods Manual,4 with age-, sex-, and race-specific distribution location of lipid and lipoprotein levels in stroke kindreds (table) determined using population data from the Lipid Research Clinic’s Laboratory Methods Manual,4 where lipids-lipoproteins were quantitated using identical laboratory methods. The absolute values for lipids and lipoproteins in the pediatric stroke probands and their families along with age-sex-race-specific “normal” population ranges have previously been published.5

Neuroradiologic and Neurologic Evaluation

Seven of the original eleven children (#s 1–7, table), and the new subject, #8, had brain angiography performed shortly (less than 48 hours) after the onset of their stroke.

The mediastinal and cervical carotid arteries were systematically visualized during angiography, while the aorta was not assessed.

After our initial documentation of the presence of familial lipoprotein abnormalities in these kindreds,2 3 we submitted the 7 available cerebral angiograms (subjects 1–4, 6, 7, table) for retrospective interpretation by an neuroradiologist who was unaware of the familial lipoprotein abnormalities, had not reviewed previous radiologic diagnostic conclusions, and had no knowledge of the clinical histories.

Results

Lipids, Lipoproteins, and Family History of Atherosclerotic Coronary and Cerebrovascular Disease

As displayed in the table, and as previously reported,2 3 all eight pediatric stroke probands had abnormalities of lipids and lipoproteins, with six of eight having low levels of C-HDL. In addition, premature myocardial infarction and/or stroke were consistently present in their adult relatives (table). None of the 8 kindreds were free of premature atherosclerotic vascular disease in adults; affected family members usually had sustained morbid or lethal myocardial infarction or stroke at or before age 60 (table).

Stroke Events, Sequelae, and Residuals, Retrospective Angiographic Interpretations

The table displays the age of stroke onset, current age, time of stroke recovery, and neurologic residuals,
if any. More detailed clinical and radiological descriptions of the subjects follow below.

Subject #1 was a 19-month old male who was well until two days prior to admission when his mother noted that he was stumbling and falling to his right side. Twenty-four hours prior to admission he became irritable and disoriented. On the day of admission he was examined by an otolaryngologist because of severe vertigo and was subsequently admitted to Children’s Hospital Medical Center (CHMC) for neurological evaluation which revealed right hemiparesis. The right hemiparesis improved gradually, and six months after admission there were no residual neurological findings.

The neuroradiologist interpreted the angiogram as definitely abnormal: “There is a tortuous left internal carotid, with mild (approximately 40%) stenosis of the left middle cerebral artery and minimal narrowing of the A-1 section on the left. There is also evidence of elongation of vessels, and there is tortuosity of the right internal carotid.”

Subject #2, a 13-year old male, suffered the acute onset of a right frontal headache and left sided weakness. He was sitting, talking on the telephone at the time of onset of symptoms, fell to the floor, but remained coherent. On admission to CHMC he had a left hemiparesis. His symptoms and signs resolved over a 24-hour period in the hospital.

The neuroradiologist gave the following interpretation: “There is a prominent loop of the right internal carotid at C-1. There is a small subtle filling defect in the medial posterior wall of the right internal carotid just above the anterior clinoid level.” The differential diagnosis for this lesion included localized atheroma-tous plaque, or thrombus, congenital web, or a focal site of dissection. There was also intermittent filling of the anterior cerebral artery suspicious of a low pressure system. It was felt that the vessels were more tortuous than expected for the age of the patient.

Subject #3, a 7-year old male, arose from his bed in the evening and fell to the floor with right sided weakness. On admission to CHMC he had right motor hemiparesis and expressive dysphasia. The degree of hemiparesis and slurred speech fluctuated and then improved over 24 hours. There was full recovery in 21 days.

The neuroradiologist reached the following conclusion: “There is minimal narrowing of the left supraclinoid internal carotid artery, and 35–40% narrowing of the A-1 segment. There is also a deep inferior parietal branch of the middle cerebral artery which looks attenuated and may be recanalized.”

Subject #4, a 6½-year old male, complained of a sudden severe bifrontal headache when he was taking a bath. When he tried to get out of the bathtub, he was unable to move the left side of his body. He was taken to CHMC where physical examination revealed a left hemiparesis and left homonymous hemianopia. The hemiparesis gradually improved, but the subject was left with a permanent residual deficit of left spastic hemiparesis.

The neuroradiologist interpreted the radiographs as showing minimal narrowing of the right internal carotid artery, no filling of the A-1 segment of patient’s anterior cerebral artery, and beading and narrowing of the middle cerebral artery from the origin to the trifurcation.

Subject #5, a 11½-year old female, slumped over while sitting on the bleachers during gym class. Her teacher observed slurred speech and a limp right arm and leg. On admission to CHMC she had a right hemiparesis and dysphasia. She improved in the hospital, but on the third day of hospitalization, she had a repeat episode of right sided weakness, with accompanying dysphasia. She gradually improved over the next eight months at which time she had no neurological residual.

The angiograms were initially read as demonstrating arteriopathy with beading, vascular occlusion, and tortuosity, involving the horizontal portion of the left middle cerebral artery and the middle cerebral supply to the parietal region. These films were not available for retrospective review.

Subject #6, a 13 ½-year old male, developed an unremitting and disabling headache. When this persisted for 24 hours, he was referred to the CHMC where, on admission, his physical examination was normal, but on the second hospital day he developed acute left hemiparesis. This resolved gradually over the next fourteen days.

The neuroradiologist reached the following conclusion: “There is a diffuse abnormality involving both the large and medium sized intracranial arteries. Most of the lesions are constricting, but a few show luminal widening. These findings are ordinarily associated with arteritis in children but might be interpreted as arteriosclerosis in an adult.” The changes were described as lesions similar to those often found in an acute inflammatory process, and in diabetic patients, but also seen in adult patients with arteriosclerosis.

Subject #7, a 6½-year old female, complained she could not stand on her left leg. This lasted approximately forty minutes and then resolved. Later that evening she complained she could not walk, and her mother noted that her left arm seemed “paralyzed.” She was taken to CHMC where a left hemiparesis was found on physical examination. Her neurological status then returned to normal over a fourteen-day period with function returning to her leg first and to her arm later.

The neuroradiologist concluded that the right common and internal carotid arteries were normal. Occlusion of the ascending frontoparietal branch of the left middle cerebral artery was noted. The left vertebral angiogram was interpreted as normal.

Subject #8, a 13 ½-year old female, sustained a sharp left temporal headache while lifting a fifty pound bag of cement. This was followed by right hemiparesis with expressive aphasia. On admission to CHMC she had a right hemiparesis with a hemisensory deficit and expressive dysphasia. The symptoms gradually resolved, but at one month after her acute event she retained mild right-sided weakness with hyperreflexia.
The neuroradiologist noted that there was irregular mild narrowing of the left supraclinoid internal carotid artery and occlusion of a middle cerebral branch in the left temporal-parietal region (fig.). Late retrograde filling of a wedge-shaped segment of the left parieto-occipital area was noted, and is indicative of collateralization to the area.

As displayed in the table, there were varying numbers of years of follow-up since the stroke event. None of the children have sustained a second stroke. The majority have, as summarized in the table, regained their pre-morbid normal status. Prospective longitudinal follow-up of these and future cases will be needed to ascertain the prevalence of future events, either cerebral or coronary, in these pediatric stroke probands and their families.

Discussion

The neuroradiologist retrospectively interpreted 6 of the 7 studies as abnormal. The arteriopathy observed was non-specific. Without antecedent clinical information beyond the fact that these children had ischemic strokes, the neuroradiologist would have considered the following differential diagnoses: sickle cell disease, other hemoglobinopathies, drug abuse, embolic phenomena secondary to congenital heart and/or cardiac valvular disease, collagen vascular disease, and polycythemia. By the selection criteria for this study, none of the above diseases were present in this group of children, and, under this circumstance, the radiologic diagnosis of fibromuscular dysplasia would commonly be made. A previous report of hemiplegia in children due to fibromuscular dysplasia revealed segmental narrowing and adjacent aneurysmal dilatation, giving a "string of beads" picture that has become the angiographic hallmark of the disease and allows a presumptive diagnosis. The vascular occlusion, irregularities of the arterial lumen, beading, tortuosity, and evidence of collateralization repetitively observed in our subjects were not felt to represent...
fibromuscular dysplasia but, speculatively raised the diagnostic possibility of occlusive arteriosclerosis with thrombosis. Moreover, none of the children in this study had evidence of fibromuscular dysplastic renal vessel disease, and/or progressive cerebrovascular deterioration which characterized children previously reported to have fibromuscular dysplasia.6 Within this frame of reference it might be important to measure lipids and lipoproteins in children who had a previous radiologic diagnosis of fibromuscular dysplasia and/or in children with unexplained cranial arteriopathy and strokes, to determine whether or not they might have familial hyperlipoproteinemia and potentially might have cerebrovascular arteriosclerosis.

A consistent important finding was that the extracranial vasculature in all children was entirely normal. Intracranial thrombo-embolic involvement alone would appear to be a characteristic of childhood arteriosclerotic disease, a feature which should be assessed in future studies. In adult cerebrovascular arteriosclerosis, the extracranial carotid arteries are most frequently affected, particularly at the carotid bifurcation, with or without concomitant involvement of intracranial vessels, and it is somewhat unusual to have intracranial arteriopathy alone.7

Relationships between adults’ ischemic cerebrovascular disease and hyperlipoproteinemia have been well documented. Rossner et al8 recently studied 61 patients 21 to 55 years old, who presented with ischemic cerebrovascular accidents. Hypertriglyceridemia was the dominant abnormality, found in 18% of males and 17% of females. They reported that the mean value of C-HDL was 18% lower in the stroke subjects than in a matched control group, and noted that the C-HDL concentrations were lower than expected by virtue of the very low density lipoprotein triglyceride concentration alone. Three other studies have demonstrated low levels of C-HDL and/or high levels of triglyceride in adults with non-hemorrhagic cerebrovascular accidents.9-11 Thus, lipoprotein patterns of children in this series are similar to those found in the studies of adults with CVAs.8-11

In our initial report on the association of abnormal lipoprotein patterns and childhood stroke,2-3 we speculated that lipoprotein abnormalities could be related to endothelial damage and thrombosis of cerebral arteries. There is in vitro evidence to support this hypothesis. In a recent in vitro study by Tauber et al,12 high density lipoprotein had a protective and restorative effect on bovine vascular endothelial cells, while low density lipoproteins were toxic for the same cells. If this process occurs in vivo, low C-HDL and/or high C-LDL and triglyceride may predispose to endothelial damage and thrombus formation, as observed in this report. Low C-HDL may also fail to restore the integrity of endothelial cells once they are injured.12 Fleisher et al13 demonstrated that high density lipoproteins stimulate prostacyclin synthesis in cultured arterial endothelial cells, possibly by providing them with arachidonic acid.13 We speculate that, in the presence of low C-HDL in humans, arterial endothelial cell synthesis of prostacyclin might be depressed,13 and, as a consequence, both arterial spasm and likelihood of endothelial platelet aggregation might be increased, enhancing the likelihood of localized thrombosis and obstruction.

We postulate that the absence of occlusive, atherosclerotic, carotid plaques in our subjects further points to some form of intracranial artery arteriopathy, rather than to the presence of mature, advanced atherosclerotic lesions. The identification of the basic vascular lesion as arteriosclerotic, and the opportunity to examine the endothelium for damage12 and for synthesis of the vasoactive prostaglandins13 must await post-mortem confirmation. As noted before, the angiographic findings are not specific for arteriosclerosis; the arteriopathy observed was non-specific.

We conclude that the apparent association of lipoprotein abnormalities and strokes in children and their families merits further exploration. In such children, the arterial abnormalities demonstrated radiologically, would, speculatively, appear to have an arteriosclerotic basis, within the caveats presented above.

Population studies have shown that C-HDL has an independent, highly significant, and inverse relationship to coronary heart disease risk.14,15 In the face of familial aggregation of low C-HDL and/or elevations of triglyceride or C-LDL, the first and second degree adult relatives of pediatric stroke probands would have been expected to reveal a considerable amount of premature coronary heart disease and ischemic cerebrovascular disease. This expectation was realized in the observation of premature coronary heart disease and/or ischemic cerebrovascular disease in adult relatives of the stroke probands in all eight kindreds. We speculate that accelerated familial clustering of premature ischemic stroke and atherosclerotic coronary heart disease may reflect not only familial dyslipoproteinemas, as in this report, but that future studies may also reveal familial apolipoprotein abnormalities, including low or absent apoAI, the major apolipoprotein of high density lipoprotein.2,16

Children with unexplained ischemic cerebrovascular accidents should have lipid and lipoprotein determinations; the diagnostic possibility of occlusive intracranial arteriosclerosis must be entertained. Strong consideration should be given to performing cerebral angiograms to best delineate possible arteriopathy. Computerized tomography alone is insufficient to make the diagnosis of occlusive cerebral arteriopathy.

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Non-Invasive Evaluation of Patients with Extracranial to Intracranial Bypass

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SUMMARY In selected patients with cerebrovascular insufficiency, an extracranial-intracranial bypass is indicated to increase cerebral blood flow. To assess the effect of this operation upon routine non-invasive testing, 15 patients had oculoplethysmography, carotid phonoangiography and Doppler testing. None of those with a preoperative abnormality were changed after surgery, despite angiographically proven anastomotic patency. Whereas non-invasive tests may correctly identify severe internal carotid stenosis, use of these modalities in their routine form does not predict extracranial-intracranial bypass patency.

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IN 1966 DONAGHY AND YASARGIL' reported on microvascular extracranial-intracranial bypass (EC-IC) for distal cerebrovascular lesions. Since then this procedure has been utilized in selected patients to bypass middle cerebral artery lesions, internal carotid siphon stenosis and internal carotid occlusion. In 1977 the Peripheral Vascular Lab at the Loyola University Medical Center began to evaluate a series of EC-IC patients pre- and post-operatively. Specifically, we hoped that routine noninvasive cerebrovascular testing could assess EC-IC bypass patency. The following is a report of our experience.

Methods and Materials

A battery of three non-invasive tests — supraorbital Doppler ultrasound evaluation, carotid phonoangiography, and oculoplethysmography (Kartchner) — were performed on each patient. In our laboratory this multiple modality testing detects 85% of carotids with > 75% stenosis and is normal in 94% of carotids with < 50% stenosis.

In the Doppler evaluation, a pencil probe is placed over the frontal artery. Direction of flow and signal response to sequential compression of the superficial temporal, facial, intraorbital and common carotid arteries is noted. Normally ophthalmic artery flow and hence frontal artery flow is antegrade out of the eye and is not effected by digital compression of the extracranial carotid artery branches. If compression of an extracranial carotid branch (frontal, infra-orbital, superficial temporal artery) reduces the audible signal, a functioning collateral is demonstrated. An absence of signal diminution to common carotid compression likewise indicates an abberant source of ipsilateral frontal artery blood flow (i.e. contralateral carotid or vertebral arteries). An abnormal response equates to a > 75% ipsilateral internal or common carotid area stenosis.

Phonoangiographic assessment of cervical bruits and oculoplethysmographic evaluation of ocular pulse volume changes as described by Kartchner et al.3 are

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