review

Cardiovascular disease in neurofibromatosis 1: Report of the NF1 Cardiovascular Task Force

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Purpose: Patients with neurofibromatosis 1 (NF1) are at increased risk for a variety of cardiovascular disorders, but the natural history and pathogenesis of these abnormalities are poorly understood. **Methods:** The National Neurofibromatosis Foundation convened an expert task force to review current knowledge about cardiovascular manifestations of NF1 and to make recommendations regarding clinical management and research priorities related to these features of the disease. **Results:** This report summarizes the NF1 Cardiovascular Task Force's current understanding of vasculopathy, hypertension, and congenital heart defects that occur in association with NF1. Recommendations are made regarding routine surveillance for cardiovascular disease and diagnostic evaluation and management of cardiovascular disorders in individuals with NF1. **Conclusion:** Our understanding of the natural history and pathogenesis of cardiovascular disease in NF1 has improved substantially in the past few years, but many clinically important questions remain unanswered. ***Genet Med* 2002:4(3):105–111.**

Key Words: *neurofibromatosis 1, vasculopathy, hypertension, congenital heart defects*

Neurofibromatosis 1 (NF1), an autosomal dominant disease, is one of the most common mendelian disorders.[1] It is characterized by extremely variable expressivity, but most patients have café-au-lait spots, intertriginous freckling, dermal and plexiform neurofibromas, and learning disabilities.[2] People with NF1 may also develop cardiac and vascular disease, but the frequency, natural history, and pathogenesis of these abnormalities are uncertain. The National Neurofibromatosis Foundation convened an expert panel, the NF1 Cardiovascular Task Force, to review current knowledge about the cardiovascular manifestations of NF1 and to make recommendations regarding clinical management and research priorities. This is the report of that Task Force.

Neurofibromas, the characteristic tumors of NF1, can develop within the heart, obstruct blood flow in the heart or major vessels by compression or invasion, or erode a vessel and cause hemorrhage. Fortunately, these are rare complications. This report will concentrate on the three most common cardiovascular manifestations of NF1, viz., vasculopathy, hypertension, and congenital heart defects.

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Received: November 16, 2001.

Accepted: February 15, 2002.

People with NF1 constitute a substantial fraction of all patients with dysplastic renal artery stenosis,[3] early-onset cerebrovascular disease,[4] or pheochromocytomas,[5] and cardiovascular disease is a frequent cause of premature death in individuals with NF1. Sørensen and associates[6] found that myocardial infarction and cerebrovascular accidents often occurred at a younger than expected age among NF1 patients. Zöller et al.[7] reported that cardiovascular disease, hemorrhage, and embolism were frequent causes of death in 70 adult NF1 patients who were followed for 12 years. Hypertension was significantly associated with mortality, and the mean age at death among the NF1 patients was approximately 14 years younger than expected. The median age of death reported on death certificates of 3,253 individuals with probable NF1 was approximately 15 years less than expected in another study.[8] Diagnoses suggestive of NF1 vasculopathy were listed 7.2 times more often than expected among NF1 patients < 30 years old and 2.2 times more often than expected among those who were 30 to 40 years old at the time of death.

NF1 VASCULOPATHY

Epidemiology and clinical features

NF1 can cause a vasculopathy, but the frequency is unknown. Symptomatic involvement is uncommon,[9] and many affected patients remain asymptomatic throughout life.[10] NF1 vasculopathy may affect vessels ranging in size from the proximal aorta to small arterioles and may produce vascular stenosis, occlusion, aneurysm, pseudoaneurysm, rupture, or fistula formation.[11] The systemic arterial circulation is usually affected, but involvement of the veins or pulmonary arteries has been reported. Most NF1 patients with vasculopathy have

multiple affected vessels. NF1 vasculopathy is usually recognized in childhood or early adulthood, often in association with pregnancy.

The renal arteries are the most frequent sites of symptomatic vasculopathy, and hypertension is the usual manifestation. Renal artery dysplasia occurs in at least 1% of patients with NF1.[12] Abdominal aortic coarctation may be seen in association with renal artery stenosis in NF1 patients,[13] raising the possibility that the vasculopathy and aortic narrowing may be pathogenically related.[14]

Cerebrovascular abnormalities in NF1 patients usually result from stenoses or occlusions of the internal carotid, middle cerebral, or anterior cerebral artery.[15,16] Small telangiectatic vessels form around the area of the stenosis and appear as a "puff of smoke" ("moya-moya") on cerebral angiography[17] (Fig. 1). Intracranial aneurysms and cervical arteriovenous fistulae and aneurysms may also occur in NF1 patients but are less common and tend to be seen in older patients.[18]

NF1-associated cerebrovascular disease is most often diagnosed in children who present with weakness, involuntary movements, headaches, or seizures as a result of cerebral ischemia.[4] Acute neurological deficits may reflect the formation of a thrombus or embolization. Adults present with similar symptoms, although the cause may be intracranial hemorrhage. Hemorrhage is responsible for approximately half of all deaths resulting from NF1 cerebrovascular disease.

Pathology and pathogenesis

The histopathology of NF1 vascular lesions was first described by Reubi[19] and Feyrter[20] and subsequently classified by Salyer and Salyer[10] and by Orcel and Chometter.[21] The classifications are based on vessel diameter, histology, and morphology (Table 1). Both classification systems focus on the common histological features of small artery disease—abnormal proliferation of spindle cells in the wall, degeneration, healing, and subsequent muscle loss accompanied by extensive fibrosis. The process may culminate in formation of micronodular smooth muscle aggregates in the vessel wall.[22] Mixed, intermediate, and variant forms occur in many cases, suggesting that these lesions are pathogenetically related.[10] All may result from cellular proliferation in the wall, with the differences reflecting variations in severity, maturation, and extent of healing.

Feyrter[20] proposed that NF1 vascular lesions develop by proliferation of nerves within affected vessel walls, whereas Reubi suggested an origin from non-nervous tissue.[19] Greene et al.[23] and Huffman et al.[22] observed that Schwann cell proliferation dominates large vessel disease, whereas mesodermal dysplasia or fibromuscular hyperplasia is most important in the small artery vasculopathy. Large vessel disease usually terminates with rupture as a result of compressive force from surrounding ganglioneuromatous or neurofibromatous tissue. In contrast, small vessel disease usually presents as a stenotic or occlusive lesion that lacks an obvious neural component. Small vessel lesions appear to be composed of smooth muscle nodules (Figs. 2 and 3) that arise from the walls of the arteries themselves.[23,24] Fibromuscular hyperplasia and neural proliferation in vessel walls may exist at different stages of disease progression.

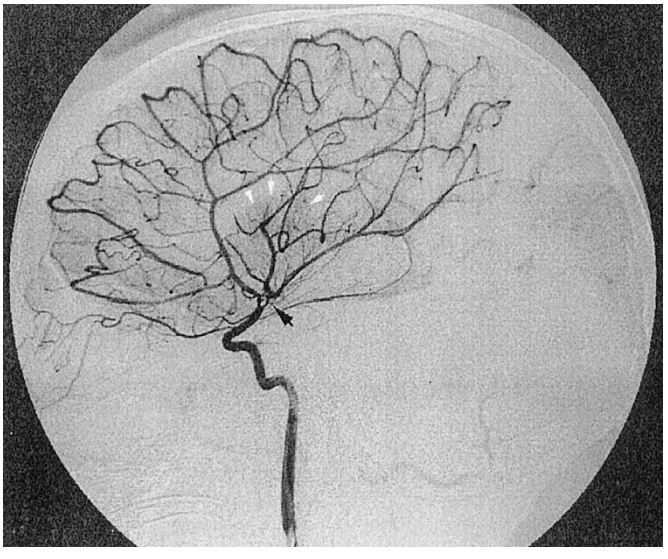

Fig. 1 A cerebral arteriogram illustrates the moya-moya ("puff of smoke") appearance in small telangiectatic blood vessels that surround the stenosis at the level of the internal carotid artery in a patient with NF1. Telangiectatic blood vessels are denoted by the "blush" of radiographic contrast dye (white arrows) surrounding the internal carotid artery occlusion (black arrow). Photograph provided by Dr. Bruce Korf, taken from Gutmann.[4]

Table 1
Histological classification of NF1 arterial lesions

Purely intimal (circumscribed)
50–400 μm
Intimal proliferations/stenosis
Medial thinning
Normal adventitia
Intimal aneurysm (circumscribed)
500–1000 μm
Glycosaminoglycan-rich intimal thickening
Elastic disruption/medial loss
Normal adventitia/small aneurysms
Arterial nodules (nodular)
100–700 μm
NF nodules of 300-μm diameter between media and adventitia
Protrudes into intima/stenosis
Epithelioid (diffuse)
200–700 μm
Spindle cell proliferation throughout wall
Stenosis

Modified from Huffman et al. [22]

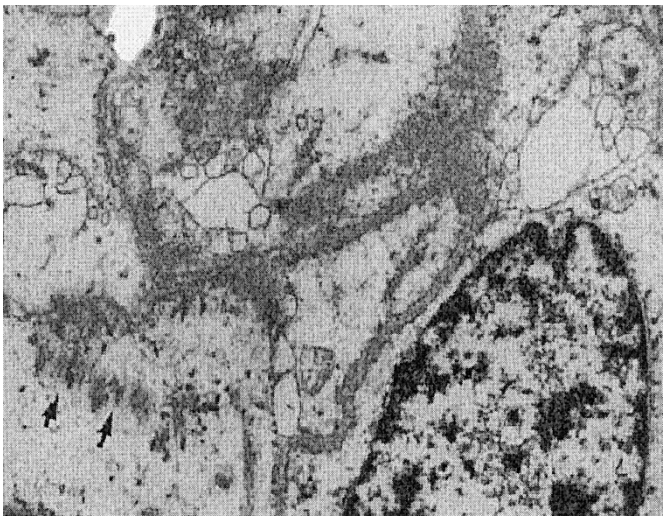

Fig. 2 Electron micrograph of a myofibroblast-like cell with a cleaved nucleus, prominent nucleoli, and cytoplasmic dense bodies, taken from an affected muscular artery. Reprinted from Finley and Dabbs[12] with permission.

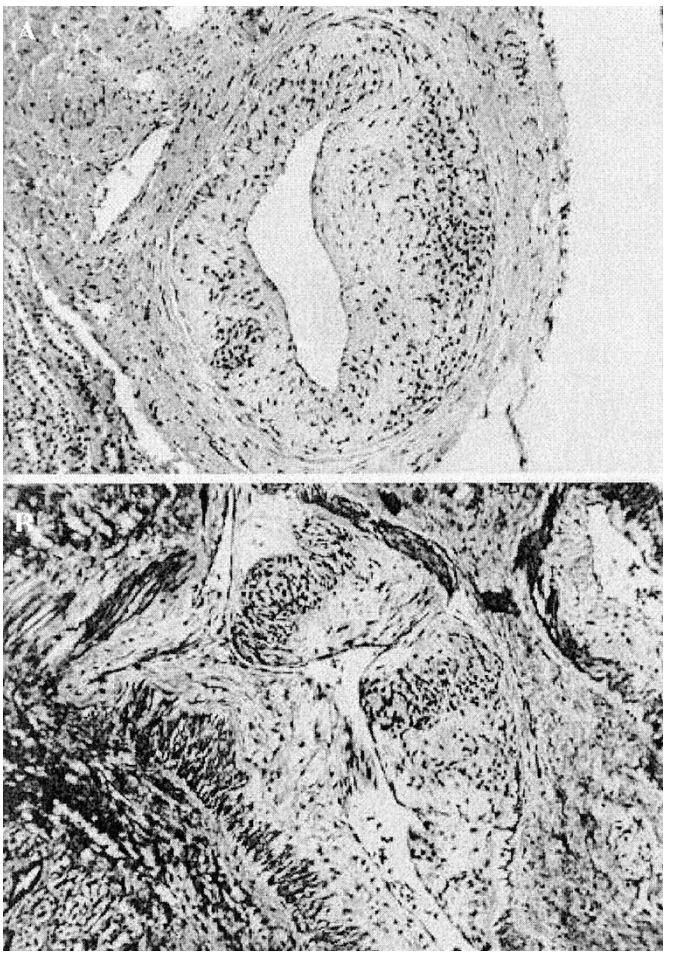

Fig. 3 Photomicrographs of cross-sectionally (A, hematoxylin and eosin; original magnification, ×170) and somewhat obliquely sectioned (B, hematoxylin and eosin; original magnification, ×170) vessels demonstrating thickened intima and the presence of several smooth muscle cell nodules. Reprinted from Greene et al.[23] with permission.

Management

The accuracy of noninvasive diagnostic tests such as captopril renal scans or renal ultrasound examinations to detect renal artery stenosis in NF1 patients with renovascular hypertension has not been studied. The possible coexistence of multiple forms of NF1 vasculopathy in any given patient (e.g., stenosis of the renal artery and saccular aneurysm of intrarenal vessels) further complicates interpretation of these diagnostic tests. Therefore, we recommend renal arteriography as the preferred test for renal artery stenosis in patients with NF1 and hypertension. For patients who cannot tolerate arteriography, e.g., those with impaired renal function, we recommend magnetic resonance angiography as an alternative imaging modality. Magnetic resonance angiography can detect atherosclerotic stenosis of the main renal artery accurately but does not reliably identify significant stenosis of accessory renal arteries,[25] which is why we recommend it only in NF1 patients who cannot tolerate direct arteriography.

It is important to recognize that NF1 patients found to have an anatomic narrowing of the renal artery do not necessarily have renovascular hypertension, and correction of the narrowing may or may not correct the elevated blood pressure. This uncertainty is because of the high incidence of essential hypertension in NF1 patients and the difficulty in identifying anatomic lesions that are causally related to high blood pressure. Thinning of the renal cortex and discrepancy in renal length when comparing a kidney with a stenotic lesion to the contralateral nonstenotic kidney are helpful in identifying patients with an increased likelihood of having renovascular hypertension. Renal vein renin sampling may also have a role in this setting.[26]

"Moya-moya" is a rare complication of NF1, and no information is available that justifies a diagnostic approach in NF1 patients that is different from that used in people with "moya-moya" disease who do not have NF1. Therefore, we recommend use of the general guidelines for diagnosis and treatment of "moya-moya" disease that have recently been formulated.[27] The diagnosis is typically based on cerebral angiography, demonstrating bilateral stenosis or occlusion at the terminal portion of the internal carotid artery and/or the proximal portion of the anterior or middle cerebral arteries in proximate association with abnormal vascular networks.

NF1 patients of any age who present with a neurological deficit of sudden onset should be evaluated promptly for cerebrovascular disease. Initial assessment includes brain imaging. Cerebral angiography may also be appropriate when the history and magnetic resonance imaging (MRI) suggest deficits in a vascular distribution. Magnetic resonance angiography may eventually supplant conventional cerebral angiography for the evaluation of NF1 patients. Because "moya-moya" is etiologically heterogeneous, other causes should be eliminated before attributing cerebral vascular disease to NF1 vasculopathy. Treatment of cerebrovascular abnormalities in individuals with NF1 is identical to that in other patients and may include both surgical and medical options.

HYPERTENSION

Epidemiology and clinical features

Hypertension is common among NF1 patients, and the prevalence increases with age.[28,29] High blood pressure is especially frequent in women with NF1 during pregnancy.[30] Essential hypertension is the most common form in adults with NF1, but it is uncertain whether essential hypertension is a feature of NF1 or just a coincidental disease that is often recognized during medical evaluation for other reasons.

Renal artery stenosis from NF1 vasculopathy is a well-documented cause of hypertension.[31] It usually presents in childhood or young adulthood, often during pregnancy. Pheochromocytomas are an uncommon cause of hypertension, but they occur in 0.1 to 1.5% of older patients with NF1.[32]

Management

Although hypertension among people with NF1 is usually "essential," thoughtful evaluation for identifiable secondary causes is necessary. Children with hypertension and/or discrepancies in pulses or blood pressures between upper and lower extremities should be screened for aortic coarctation. Renovascular disease should be considered in any child or young adult, and particularly in any pregnant woman, with hypertension and NF1. Renovascular hypertension is less likely in older NF1 patients but should be considered if the hypertension is severe or refractory to treatment or if an upper abdominal bruit is heard.

Given the potential for poor outcome in patients with undiagnosed pheochromocytoma[33] and the sensitivity of biochemical testing, clinicians should consider evaluation for pheochromocytoma in all NF1 patients who develop hypertension during pregnancy and those with refractory hypertension or symptoms of catecholamine excess. The diagnosis is confirmed by imaging studies and measurement of urinary or plasma catecholamines. Both plasma and urinary catecholamines have been shown to be highly sensitive and specific for pheochromocytoma,[34,35] but accurate measurement of plasma catecholamines requires strict adherence to research center protocols for patient preparation and blood sampling. Therefore, we recommend the more straight-forward measurement of 24 hour urinary excretion of catecholamine metabolites (metanephrines and vanillylmandelic acid) and total plus fractionated catecholamines. In patients who have positive biochemical tests, MRI or computed tomography can be used to localize the pheochromocytoma. Imaging studies may be confusing in patients who do not have biochemical evidence of pheochromocytoma because biologically insignificant adrenal adenomas may be identified incidentally. Administration of radiographic contrast medium should be avoided in patients who have a positive biochemical screen because of the potential for contrast medium to increase catecholamine output from chromaffin cell. An association has been observed between the occurrence of pheochromocytomas and carcinoid tumors in NF1 patients,[36] so pheochromocytoma should be sought if a carcinoid tumor is found and a carcinoid should be sought if a pheochromocytoma is found.

Although patients with NF1 appear to be at increased risk of cardiovascular-associated morbidity and mortality,[7] outcome data are not available to support recommending a lower target blood pressure than in the general population. Goal blood pressure for patients without target organ damage or diabetes should, therefore, be 140/90 mm Hg, as in the general population. For patients with end organ damage and/or diabetes, goal blood pressure should be 130/85 mm Hg.[37]

Renal artery angioplasty for stenotic lesions appears to have a lower success rate in NF1 patients than in non-NF1 patients.[38] Surgical revascularization or nephrectomy frequently produces improvement in blood pressure in such patients, but nephrectomy should be reserved for those with parenchymal lesions or severe disease of the renal artery that prevents grafting. The high incidence of essential hypertension among NF1 patients probably contributes to surgical treatment failures because essential hypertension cannot be diagnosed with certainty on a prospective basis. Treatment of pheochromocytoma includes alpha-adrenergic blockade, beta-adrenergic blockade if needed to control heart rate or arrhythmias, and surgical removal.[39]

CONGENITAL HEART DEFECTS

Epidemiology and clinical features

The frequency of congenital heart defects (CHD) ranges from 0.4 to 6.4% in published series of NF1 patients.[14] It is not clear that all of the patients in these reports fulfill currently accepted criteria for diagnosis of NF1 or that all of the reported cardiac abnormalities are bona fide CHD. A recent review of 2,550 NF1 patients in the National Neurofibromatosis Foundation International Database found 50 (2%) with CHD. In 42 of these patients (1.6% of the total), CHD was confirmed by an appropriate imaging test.[14] Most studies report a 0.4 to 0.9% incidence of CHD among liveborn infants in the general population.[40] These studies are not strictly comparable to the NNFF International Database or other reported series of NF1 patients ascertained through specialty clinics. Nevertheless, the available data are consistent with a higher than expected frequency of CHD among NF1 patients. The strongest evidence that NF1 and CHD are, in fact, associated, is the extraordinarily high proportion of these patients in whom the CHD is pulmonic stenosis, usually of the valvar type.

Pulmonic stenosis is a recognized feature of three uncommon clinical subtypes of NF1[14]—Watson syndrome, NF1-Noonan syndrome, and individuals with large deletions of the *NF1* gene. Pulmonic stenosis is also unusually frequent among patients with NF1 who do *not* have these clinical subtypes, accounting for approximately one quarter of all CHD among NF1 patients.[14]

Perhaps as important as the predominance of pulmonic valve stenosis among NF1 patients is the low frequency of more complex CHD, including conotruncal defects.[14] This finding is somewhat surprising, because double outlet right ventricle, a

conotruncal defect, occurs in homozygous *Nf1* "knockout" mouse embryos.[41,42] The NNFF International Database series of 2550 NF1 patients included two with tetralogy of Fallot, which is considered a conotruncal CHD.[14] There were no atrioventricular canal, looping, or laterality defects.

Left heart obstruction (aortic stenosis or coarctation) was reported in 7 of 50 NF1 patients with CHD from the NNFF International Database.[14] Five of these patients had coarctation, and in at least three, the aortic narrowing was of a long fusiform type, which differs anatomically from the abrupt segmental constriction that is usually seen in patients who do not have NF1.

Pathology and pathogenesis

The involvement of neurofibromin in cardiac development is strongly supported by *Nf1* "knockout" mouse models.[41,42] Homozygous *Nf1* mutant embryos succumb before Day 14 of gestation with double outlet right ventricle and associated abnormalities of cardiac outflow tract formation, endocardial cushion development, and myocardial structure. In some cases, the enlarged endocardial cushion tissue appears to obstruct forward blood flow and produce severe venous congestion. This finding is reminiscent of the valvar pulmonic stenosis seen in human NF1 patients. *Nf1* is expressed by myocardial cells and by mesenchymal cells of the endocardial cushions. Explanted endocardial cushions from mutant embryos display exuberant epithelial–mesenchymal transformation when cultured on collagen gels designed to mimic the process of cushion formation in vivo. Epithelial–mesenchymal transformation and endocardial cushion formation are complex processes that involve signals from the overlying myocardium, where *Nf1* is also expressed, and migrating neural crest cells that populate the endocardial cushions may influence mesenchymal cell proliferation and/or apoptosis as well. Hence, the precise cell type and molecular function of neurofibromin that result in endocardial cushion defects in homozygous *Nf1* knockout mice remain to be clarified.

Management

All patients with NF1, especially those with the Watson or NF1-Noonan phenotypes, should have a careful cardiac examination with auscultation and blood pressure measurement. Four extremity blood pressure measurements should be considered in children suspected of having aortic coarctation. Any patient with a suspicious heart murmur should be evaluated by a cardiologist and examined by echocardiography for pulmonic stenosis, aortic coarctation, or other CHD. If a CHD is found, subsequent follow-up and treatment should be based on the age of the patient and the nature and severity of the lesion.

EMERGING PATHOGENETIC AND MOLECULAR INSIGHTS

NF1 is a large gene, spanning approximately 335 kb of chromosome 17q11.2.[43] The protein product, neurofibromin, is an activator of $p21^{ras}$ GTPase, which in turn fosters the conversion of $p21^{ras}$- GTP to inactive $p21^{ras}$-GDP, thereby suppressing cell growth. *NF1* mutations reduce this suppression and promote cellular proliferation. Certain neoplasms, including malignant peripheral nerve sheath tumors, gliomas, and chronic myelomonocytic leukemia, occur with increased frequency among patients with NF1.[44–47] *NF1* is thought to function as a tumor suppressor gene, and somatic loss of the second allele has been demonstrated in pheochromocytomas, malignant peripheral nerve sheath tumors, gliomas, and juvenile chronic myelogenous leukemia cells from NF1 patients.[44–47] *Nf1* haploinsufficiency also alters proliferation and survival of some cell types in the knockout mouse model.[48,49]

Neurofibromin has other functions as well. It interacts with tubulin.[50,51] The *Drosophila* homologue of neurofibromin activates an adenyl cyclase-mediated signaling pathway required for growth, learning, and memory[52]; a similar pathway may be important in humans.

Neurofibromin expression has been demonstrated in the endothelial and smooth muscle cells of blood vessels,[41,53,54] raising the possibility that NF1 vasculopathy results from abnormal neurofibromin function in endothelial or vascular smooth muscle cells or both.[55] One possibility is that deficient neurofibromin expression alters the response of vascular endothelial or smooth muscle cells to growth suppressive endothelial signals, resulting in excessive proliferation during normal vascular maintenance. Alternatively, neurofibromin deficiency might impair proliferation of endothelial cells, thereby reducing the structural integrity of the endothelium and producing secondary smooth muscle cell migration and proliferation in the vessel wall.

Although NF1 vasculopathy typically involves multiple vessels in an affected individual, the pathology is usually patchy. All of the cells in the arteries of an NF1 patient presumably have the same constitutional mutation of the *NF1* gene, so the patchiness suggests that other factors are also involved in the development of vasculopathy. Development of vasculopathy may require a "second hit" mutation of the normal *NF1* allele or a somatic mutation at one or more other loci. An attractive alternative is that local injury in the vessel wall contributes to development of these lesions, with intimal hyperplasia resulting from dysregulation of the normal repair process.[55]

The murine model of CHD caused by *Nf1* deficiency is useful for studying the role of neurofibromin in cardiac development and in cellular growth control, but these homozygous embryos may not be an appropriate model for CHD in human NF1 patients. Constitutional homozygosity for *NF1* mutations has never been reported in humans[1] and may be lethal, as it is in mice. Human NF1 patients are heterozygous for an *NF1* mutation, but CHD have not been observed in heterozygous *Nf1* mutant mice. Development of CHD in heterozygous human NF1 patients might reflect differences in murine and human dosage requirements for neurofibromin, occasional "second hit" somatic mutations of the normal *NF1* allele in a critical tissue, or effects of other genetic, nongenetic, or sto-

chastic factors that interact with neurofibromin during formation of the heart.

RESEARCH RECOMMENDATIONS

Although our understanding of the natural history, pathology, and pathogenesis of cardiovascular disease in NF1 has improved substantially during the past few years, it is still inadequate. We need to learn more about the nature and molecular basis of NF1-associated cardiovascular disease to improve our care for affected patients. Better understanding of the role of neurofibromin in embryonic development and normal function of the heart and vasculature may also provide important insights into the pathogenesis of vascular disease, hypertension, and cardiovascular malformations in the general population.

Many questions about the natural history and pathogenesis of cardiovascular disease in NF1 remain unanswered. We believe that the following research studies and resources are urgently needed to address these questions:

- A collaborative multicenter genotype-phenotype study of cardiovascular disease in NF1 patients with molecular definition of the *NF1* mutation, analysis of other possible genetic and nongenetic predisposing factors, and detailed clinical assessment of all cardiac and vascular lesions.
- Clinical studies to define the optimal blood pressure treatment level for patients with NF1 and hypertension.
- Clinical studies to determine whether particular antihypertensive medications are more appropriate for NF1 patients in certain specific clinical situations (e.g., angiotensin-converting enzyme inhibitors for patients with NF1 and renal vasculopathy).
- A multicenter cross-sectional clinical and echocardiographic study of CHD, and especially pulmonic stenosis, among patients with NF1.
- Collection protocols and a tissue bank for researchers interested in studying the pathogenesis of NF1 vasculopathy.
- Development of a good experimental model of NF1 vasculopathy in a laboratory animal or in vitro system.
- Molecular embryology studies of cardiac development in homozygous and heterozygous *Nf1* knockout mice.

Acknowledgments

The NF1 Cardiovascular Task Force was organized and sponsored by the National Neurofibromatosis Foundation. The authors thank Mr. Peter Bellermann for his assistance and support. We appreciate the journalistic assistance of Ms. Salima Harji. This report was developed while Dr. Friedman was on sabbatical leave supported by the Association of Teachers of Preventive Medicine under a cooperative agreement from the Centers for Disease Control.

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