

Neurofibromatosis type 1 and cardiac manifestations

Nörofibromatoz tip 1 ve kalple ilgili bulgular

Faruk İncecik, M.D., Özlem M. Hergüner, M.D., Sevcan Alınç Erdem, M.D.,# Şakir Altunbaşak, M.D.

Department of Pediatric Neurology, Çukurova University Faculty of Medicine, Balcalı Hospital, Adana

#Department of Pediatric Cardiology, Çukurova University Faculty of Medicine, Balcalı Hospital, Adana

ABSTRACT

Objective: Cardiac manifestations of neurofibromatosis type 1 (NF1) may include hypertension, congenital heart disease, and hypertrophic cardiomyopathy. The aim of this study was to evaluate cardiac abnormalities in patients with NF1.

Methods: Sixty-five NF1 patients (mean age: 9±4.48 years) were retrospectively studied. Standard electrocardiography and echocardiography were performed in all patients.

Results: Cardiac abnormalities were found in 11 of the 65 patients (15.3%). Five patients had mitral valve regurgitation, 2 patients had secundum atrial septal defect, 1 patient had pulmonary valvular stenosis, 1 patient had ventricular septal defect, 1 patient had tricuspid valve regurgitation, and 1 patient had aortic valve regurgitation.

Conclusion: Cardiac abnormalities have potential long-term hemodynamic consequences that justify an early diagnosis. Thus, for any patient with NF1, a cardiologic assessment is mandatory at the time of diagnosis and with regular follow-up intervals.

Neurofibromatosis type 1 (NF1) is a multisystem disease affecting 1 in 3500 people worldwide.^[1] The most frequent clinical manifestations are café au lait spots, lentiginos, and neurofibromas, with variable clinical expression.

NF1 has a broad array of clinical aspects as a result of dysplasia of mesodermal and neuroectodermal tissues.^[2] The cardiovascular manifestations of neurofibromatosis may include hypertension due to renal artery stenosis, congenital heart disease, hypertrophic cardiomyopathy, and less frequently pheochromocytoma.^[3]

Abbreviations:

ASD Atrial septal defect
NF1 Neurofibromatosis type 1
VSD Ventricular septal defect

ÖZET

Amaç: Nörofibromatoz tip 1'de (NF1) rastlanan kalp damar sistemi bozuklukları hipertansiyon, doğumsal kalp hastalığı ve hipertrofik kardiyomyopati'dir. Bu çalışmanın amacı NF1'li hastalarda kalple ilgili bozuklukları değerlendirmektir.

Yöntemler: Nörofibromatoz tip 1'li 65 hasta (ortalama yaş 9±4.48 yıl) geriye dönük olarak incelendi. Tüm hastalara elektrokardiyografi ve ekokardiyografi yapıldı.

Bulgular: Kalple ilgili bozukluklar 65 hastanın 11'inde (%15.3) bulundu. Beş hastada mitral kapak yetersizliği, iki hastada sekundum tip atriyal septal defekt, bir hastada pulmoner kapak darlığı, bir hastada ventriküler septal defekt, bir hastada triküspit kapak yetersizliği ve bir hastada aort kapak yetersizliği mevcuttu.

Sonuç: Kalple ilgili bozukluklar, uzun süreli hemodinamik sorunlara neden olabileceğinden erken tanınmalıdır. Bu nedenle, NF1'li herhangi bir hastaya tanı anında ve düzenli aralıklarla kalp değerlendirmesi zorunludur.

The aim of this study was to evaluate cardiovascular abnormalities in patients with NF1.

METHODS

Sixty-five patients from our pediatric neurology department were studied. Medical records were analyzed retrospectively for age, gender, family history, blood pressure measurement, clinical features of NF1, cerebral magnetic resonance imaging (MRI), electrocardiography, and echocardiography. None of the patients were receiving cardiac medication prior to or at time of inclusion. Electrocardiography was performed, and all patients were in sinus rhythm. The

Received: February 27, 2015 Accepted: June 03, 2015

Correspondence: Dr. Faruk İncecik. Çukurova Üniversitesi Tıp Fakültesi, Balcalı Hastanesi, Pediatrik Nöroloji Bilim Dalı, 01330 Balcalı, Adana.

Tel: +90 322 - 338 60 60 e-mail: fincecik@gmail.com

© 2015 Turkish Society of Cardiology



Table 1. Characteristics of neurofibromatosis type 1 patients

Patient no	Diagnosis	Age (year)
1	Mild mitral valve regurgitation	6
2	Mild mitral valve regurgitation	6
3	Mild mitral valve regurgitation	8
4	Mild mitral valve regurgitation	14
5	Mild mitral valve regurgitation	10
6	Mild aortic valve regurgitation	10
7	Mild tricuspid valve regurgitation	15
8	Ventricular septal defect	4
9	Secundum atrial septal defect	12
10	Secundum atrial septal defect	8
11	Pulmonary valvular stenosis	2

study protocol was approved by the local ethics committee.

RESULTS

Fifty-five patients were included in the study (37 boys, 28 girls). Thirty-nine patients had sporadic NF1, while 26 had familial form. Mean age was 9 ± 4.48 years (range: 2–16 years). Median follow-up was 3.3 years (range: 1–6 years). Cardiac abnormalities were found in 11 of the 65 patients. Five patients had mild mitral valve regurgitation without mitral valve prolapse, 1 patient had mild tricuspid valve regurgitation, and 1 patient had mild aortic valve regurgitation. Four children had congenital heart disease including secundum atrial septal defect (ASD), pulmonary valvular stenosis, and ventricular septal defect (VSD). No evidence of renal artery stenosis, hypertrophic cardiomyopathy, mitral valve prolapse, or coarctation of the aorta was observed. Blood pressure measurements were in normal limits in all patients. The characteristics of patients are shown in Table 1.

At follow-up, spontaneous closure occurred in 2 patients with ASD and in 1 patient with VSD.

DISCUSSION

NF1 is the most common neurocutaneous disease with multisystem involvement. Fifty percent of cases are transmitted by autosomal dominant inheritance, and the other 50% are caused by de novo mutations.^[4]

The NF1 gene is localized on 17q11.2 and produces neurofibromin, a GTPase-activating protein that regulates cell proliferation by inhibiting Ras activity.^[5] Neurofibromin is a ubiquitous protein which is detected in the smooth muscle layer of the aorta. Experimental studies indicate that in the absence of this protein, mouse embryo hearts develop overabundant endocardial cushions due to hyperproliferation and lack of normal apoptosis. These observations suggest the involvement of the cardiovascular system in NF1.^[6] The involvement of neurofibromin in cardiac development is strongly supported by NF1 knockout mouse models.^[7] 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 expressed, and migrating neural crest cells that populate the endocardial cushions may influence mesenchymal cell proliferation and/or apoptosis. 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.^[8]

Many reports in the literature have shown cardiac involvement in NF1, including valvular pulmonary stenosis, branch peripheral pulmonary stenosis, atrial and ventricular septal defects, coarctation of the aorta (thoracic and abdominal), and hypertrophic cardiomyopathy.^[3,9–11] In a recent study, Lin et al.^[10] reported that the prevalence rate of cardiovascular abnormalities in patients with NF1 is low (2.3%). However, in another study, Lama et al.^[11] described cardiac abnormalities in 13 of 69 patients (18.8%) with NF1. They found 4 patients with cardiac heart disease, 2 patients with mild mitral regurgitation, 2 patients with mild aortic regurgitation, 2 patients with hypertrophic

cardiomyopathy, and 1 patient with mitral valve prolapse. Tedesco et al.^[9] described cardiac abnormalities in 27% of 48 patients. They detected secundum ASD in 2 patients, mild mitral regurgitation in 2 patients, aortic valve regurgitation in 2 patients, atrial septal aneurysm in 2 patients, hypertrophic cardiomyopathy in 2 patients, mild left pulmonary artery stenosis in 1 patient, coarctation of the thoracic aorta in 1 patient, and mitral valve prolapse and mitral regurgitation in 1 patient. In the present study, cardiac abnormalities were detected in 11 of the 65 patients (16.9%). Five patients had mild mitral regurgitation, 2 patients had secundum ASD, 1 had mild aortic valve regurgitation, 1 had mild tricuspid valve regurgitation, 1 patient had VSD, and 1 had pulmonary stenosis.

Lama et al.^[11] reported 4 patients with cardiac heart disease; 2 had secundum ASD, 1 had pulmonary artery stenosis, and 1 had coarctation thoracic aorta. Additionally, in published series, the frequency of congenital heart defects ranges from 0.4% to 6.4%. In the present study, congenital heart disease was detected in 4 of the 11 patients with cardiac abnormalities.

While Sutton et al.^[12] reported a strong association between NF1 and hypertrophic cardiomyopathy, no hypertrophic cardiomyopathy was found in our patients. It is possible that it will be determined by duration of follow-up.

Patients with NF1 are at increased risk for a variety of cardiovascular disorders, but the natural history and pathogenesis of these abnormalities are poorly understood. The report of the NF1 Cardiovascular Task Force summarizes the current understanding of vasculopathy, hypertension, and congenital heart defects that occur in association with NF1.^[10]

In conclusion, recommendations are made regarding routine surveillance for cardiovascular disease, diagnostic evaluation, and management of cardiovascular disorders in individuals with NF1.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Listerick R, Charrow J. Neurofibromatosis type 1 in childhood. *J Pediatr* 1990;116:845–53. [CrossRef](#)
2. Riccardi VM. Type 1 neurofibromatosis and the pediatric patient. *Curr Probl Pediatr* 1992;22:66–107. [CrossRef](#)
3. Kurien A, John PR, Milford DV. Hypertension secondary to progressive vascular neurofibromatosis. *Arch Dis Child* 1997;76:454–5. [CrossRef](#)
4. Grifa A, Piemontese MR, Melchionda S, Origone P, Zelante L, Coviello D, et al. Screening of neurofibromatosis type 1 gene: identification of a large deletion and of an intronic variant. *Clin Genet* 1995;47:281–4. [CrossRef](#)
5. Garicochea B, Giorgi R, Odone VF, Dorliac-Llacer PE, Bendit I. Mutational analysis of N-RAS and GAP-related domain of the neurofibromatosis type 1 gene in chronic myelogenous leukemia. *Leuk Res* 1998;22:1003–7. [CrossRef](#)
6. Norton KK, Xu J, Gutmann DH. Expression of the neurofibromatosis I gene product, neurofibromin, in blood vessel endothelial cells and smooth muscle. *Neurobiol Dis* 1995;2:13–21.
7. Brannan CI, Perkins AS, Vogel KS, Ratner N, Nordlund ML, Reid SW, et al. Targeted disruption of the neurofibromatosis type-1 gene leads to developmental abnormalities in heart and various neural crest-derived tissues. *Genes Dev* 1994;8:1019–29. [CrossRef](#)
8. Friedman JM, Arbiser J, Epstein JA, Gutmann DH, Huot SJ, Lin AE, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. *Genet Med* 2002;4:105–11. [CrossRef](#)
9. Tedesco MA, Di Salvo G, Natale F, Pergola V, Calabrese E, Grassia C, et al. The heart in neurofibromatosis type 1: an echocardiographic study. *Am Heart J* 2002;143:883–8. [CrossRef](#)
10. Lin AE, Birch PH, Korf BR, Tenconi R, Niimura M, Poyhonen M, et al. Cardiovascular malformations and other cardiovascular abnormalities in neurofibromatosis 1. *Am J Med Genet* 2000;95:108–17. [CrossRef](#)
11. Lama G, Graziano L, Calabrese E, Grassia C, Rambaldi PF, Cioce F, et al. Blood pressure and cardiovascular involvement in children with neurofibromatosis type1. *Pediatr Nephrol* 2004;19:413–8. [CrossRef](#)
12. St John Sutton MG, Tajik AJ, Giuliani ER, Gordon H, Su WP. Hypertrophic obstructive cardiomyopathy and lentiginosis: a little known neural ectodermal syndrome. *Am J Cardiol* 1981;47:214–7. [CrossRef](#)

Keywords: Cardiac abnormalities; children; neurofibromatosis type 1.

Anahtar sözcükler: Kardiyak bozukluklar; çocuklar; nörofibromatoz tip 1.