CASE REPORT

# Mid-aortic syndrome with renovascular hypertension and multisystem involvement in a girl with familiar neurofibromatosis von Recklinghausen type 1

**Borivoj Petrak [1], Sarka Bendova [2], Tomas Seeman [3], Tibor Klein [4], Jiri Lisy [5], Tomas Zatrapa [1] and Tana Marikova [2]**

1. Department of Child Neurology, Charles University, 2nd Medical School and University Hospital Motol, Prague, Czech Republic
2. Institute of Biology and Human Genetics, Charles University, 2nd Medical School, Prague, Czech Republic
3. Department of Paediatrics, Charles University, 2nd Medical School and University Hospital Motol, Prague, Czech Republic
4. Cardiocenter, University Hospital Motol, Prague, Czech Republic
5. Department of Radiology, Charles University, 2nd Medical School and University Hospital Motol, Prague, Czech Republic

*Correspondence to:* Borivoj Petrak, MD., CSc.
Department of Child Neurology,
2nd Medical School, Charles University, University Hospital Motol
V Uvalu 84, 150 06 Prague 5, Czech Republic
PHONE: +420 2 24433301
FAX: +420 2 24433322
EMAIL: borivoj.petrak@post.cz

*Submitted: August 1, 2007* *Accepted: September 8, 2007*

*Key words:* **neurofibromatosis type 1; NF1 gene; exone 34; mid-aortic syndrome; renovascular hypertension; optic glioma; pubertas praecox; mental retardation**

Neuroendocrinol Lett 2007; **28**(6):734–738 **PMID:** 18063929 NEL280607C03 © 2007 Neuroendocrinology Letters • **www.nel.edu**

**Abstract**

**OBJECTIVES**: Neurofibromatosis von Recklinghausen type 1 (NF1) is an autosomal dominant neurocutaneous disorder affecting one in 3 000–4 000 individuals. Mid-aortic syndrome (MAS) is a rare condition characterized by segmental narrowing of abdominal aorta and stenosis of its major branches – mainly renal arteries, including manifestation of renovascular hypertension. MAS can be caused by different diseases, including NF1. **MAIN FINDINGS**: A 9 years old girl with primary diagnosis of NF1 combined with renovascular hypertension due to MAS, suffered of bilateral optic and chiasm glioma, pubertas praecox, speech disorder, light mental retardation and scoliosis. We have found a mutation in exone 34 of the NF1 gene (17q11.2). Her father has been also diagnosed with NF1 and hypertension developed at early age. He has the same mutation in exone 34 of NF1 gene. The girl is currently treated with conservative antihypertensive medication with positive effect. Bilateral optic and chiasm glioma are asymptomatic at the time and they had been without progress over period of time. Any vascular surgery, neurosurgical and oncological therapy are not indicated at the present time. **CONCLUSION**: This article is a summary of clinical findings in patient with NF1 due to NF1 gene mutation in exone 34. It confirms the importance of complex multidisciplinar approach to examination and taking care of NF1 patients and their families.

**Abbreviations**

| | |
|---|---|
| NF1 | - Neurofibromatosis von Recklinghausen type 1 |
| T2-TSE | - T2-weighted turbo spin echo |
| T2- TSE.F/S | - T2- weighted turbo spin echo/fat saturation image) |
| MAS | - Mid-aortic syndrome |
| FASI | - Hypersignal foci in T2-weighted images |
| DHPLC | - Denaturing high performance liquid chromatography |
| DNA | - Deoxyribonucleic acid |
| PCR | - Polymerase chain reaction |
| MLPA | - Multiplex ligation-dependent probe amplification |
| MAG3 | - Mercaptoacetyltriglycine |
| BP | - Blood pressure |
| MRI | - Magnetic resonance imaging |
| FLAIR | - Fluid attenuated inversion recovery |
| EEG | - Electroencephalography |
| ECHO | - Echocardiography |

## INTRODUCTION

The incidence of hypertension in children is reported (in the US) to be 1–5%. Renovascular disease is a frequent cause of severe arterial hypertension in childhood. The most common cause of renovascular hypertension in children is fibromuscular dysplasia involving the renal arteries (Bartosh & Aronson, 1999). About 15% of these cases are associated with neurofibromatosis von Recklinghausen type 1 (NF1). Arterial hypertension in paediatric patients with NF1 is usually due to renal artery stenosis (Estepa *et al*., 2001). A rare condition in children with renovascular hypertension is the mid-aortic syndrome (MAS) characterized by segmental stenosis of proximal abdominal aorta or distal descendent abdominal aorta combined with stenoses of its main branches – mainly renal arteries (Delis & Gloviczki, 2005). MAS can be acquired, caused by some conditions, including NF1, or congenital (Criado *et al*., 2002).

NF1 is an autosomal dominant disorder affecting one in 3 000–4 000 individuals; 40–50% of all cases are sporadic. Symptoms are highly variable. Diagnostic criteria for NF1 includes café au lait spots, axillary and/or inguinally freckling, neurofibromas and/or plexiform neurofibromas, Lisch nodules, optic glioma, distinct osseous lesions and first-degree relative with NF1. To make diagnose of NF1, it is necessary to fulfil at least two diagnostic criteria (Goldstein & Gutmann, 2004).

NF1 is caused by mutations of the gene on chromosome 17q11.2. This tumor suppressor gene encodes neurofibromin. Neoplastic processes are usually hamartomas or low grade tumours, however malignant transformation is also described (Goldstein & Gutmann, 2004). The most common tumours associated with NF1 are neurofibromas and optic gliomas (pilocytic astrocytoma grade I). Optic gliomas in NF1 occur in many (2/3) asymptomatic cases, only long-term surveillance is recommended (Listernick *et al*., 1999).

MRI of the brain also reveals multilocular hypersignal foci in T2-weighted images (FASI) localized in basal ganglia, brain stem and cerebellar white matter. These foci were present in 43%–89% children with NF1 and have non-neoplastic character. They appear to correspond with pathologic findings of areas of the myelin vacuolar change (Osborn & Salzman 2004, diPaolo *et al*., 1995).

We have introduced reliable indirect and direct NF1 molecular genetic (DNA) analysis.

Direct DNA diagnostics of NF1 with purpose of detecting specific mutations and polymorphisms is being introduced at the present time. Genomic DNA was amplified in 60 PCR fragments corresponding to 60 exons of the NF1 gene. All primers, PCR reaction conditions, temperatures for optimal heteroduplex separation and the melting domains for DHPLC were designed (Han *et al*., 2001). All detected mutations were verified by repeated PCR re-amplification and sequencing in both directions. Forward and reverse sequences were compared with the reference sequence. For detections of large duplications or inversions, the MLPA method was used. Genomic rearrangements represent only approximately 2% of all NF1 mutations (Wimmer *et al*., 2006).

This article is a summary of clinical findings in patient with NF1 due to determined NF1 gene mutation.

## CASE REPORT

The girl was born in 1998 from first physiological gravidity, birthweight 4 090 g/birthlenght 53 cm, normal adaptation. There was uneven mental and motoric development since approx. 4$^{th}$ month. She began to walk at 15$^{th}$ month of age. Speech development retardation was observed, she pronounced her first word when she was 18 month old; she has speech development disorder. Her intellectual abilities were evaluated significantly below average. Café au lait spots observed from approx. 6$^{th}$ month of age.

During a regular medical check-up at 3 years of age an elevated blood pressure (BP) was revealed (BP 150/90 mm Hg). Blood pressure on the legs was much lower then on the arms. Echocardiography (ECHO) revealed hypertrophy of the left ventricle and hypoplasy (stenosis) of the abdominal aorta. Stenosis of abdominal aorta and stenosis of both renal arteries corresponding to MAS was proved by angiography. Stenosis was located near truncus coeliacus with stricture up to 3.6 mm and 38 torr gradient. Below the stenosis the diameter is 4.7 mm (Figure 1). Stenosis involved the origin of the right renal artery (100/84 torr), on the left side stenoses on the middle part of the renal artery were noted. Dynamic renal scintigraphy with MAG3 without and after captopril revealed bilateral pathology with signs of significant stenosis of arteries supplying upper and middle part of left kidney. Her plasma creatinine level and estimated glomerular filtration rate were normal. Basal plasma renin activity in supine position was 3.596 μg/l/hr. (normal range 0.5–1.5), stimulated level was 15.064 μg/l/hr. (normal 0.7–2.6) and basal aldosteron level was 738 ng/l (normal 25–130). She had mild proteinuria and normal level of vanilmandelic acid in her urine. Her hypertension was controlled by quadruple antihypertensive medication (atenolol, amlo-

dipine, prazosin and minoxidil). BP gradually decreased (110–120/60–75 mm Hg). Similar results were obtained during ambulatory 24-hr BP monitoring at daytime.

She had no headache or abdominal pain and her renal function was normal during this therapy. Surgical treatment such as bypass between thoracic and abdominal aorta and bypass of right renal artery has been considered, however it haven't been performed yet due to satisfactory results of antihypertensive therapy.

The girl has positive family history. Her father had been diagnosed, according to dermal findings, with NF1 when he was 20 years old and he developed hypertension when he was 35. Our patient has no siblings.

During initial hospitalization (in 2001) the girl had been diagnosed as NF1 patient. NF1 diagnosis was confirmed by MRI examination of the brain, which showed gliomas of both optic nerves and optic chiasm (Figure 2). Multiple FASI on T2-weighted turbo spin echo (T2-TSE) and fluid attenuation inversion recovery (FLAIR) images in characteristic localisation in white matter of temporal lobes, basal ganglia and thalamus bilaterally, pons and white matter of cerebellum were observed (Figure 3).

During the last neurological examination a light mental retardation, speech development disorder, central hypotonic syndrome, dysmorphic facial traits, macrocephaly, scoliosis and abnormal shape of thorax were noted. She had skin picture characteristic for NF1 – multiple café au lait spots, axillary and inguinally freckling and probably plexiform neurofibromas.

Follow up MRI of brain at the end of 2005 showed no significant progress of the pathological changes, including gliomas of optic nerves and chiasm. Gliomas are asymptomatic. Slight papillary atrophy on the eyeground is probably consequence of I.grade hypertensive retinal angiopathy. The girl is also under surveillance of oncologist because of gliomas, but no oncotherapy and no neurosurgical treatment have been indicated. She has signs of the pubertas praecox. Ophthalmologic examination revealed iridial hamartomas – Lisch nodules.

Evoked potentials showed abnormal findings on electroretinography, normal response latency on visual evoked potentials and abnormal finding on brainstem auditory evoked potentials. There are no epileptiform graphoelements on EEG, sleep EEG is without pathology.

The girl and her family underwent genetic examination. Direct molecular genetic analysis of NF1 with purpose of detecting specific mutations and polymorphisms was used. We used the PCR, DHPLC and MLPA methods. In our patient a mutation in exone 34 (c.6473_6474insGAAG), was detected. The mutation c.6473_6474insGAAG causes translation of the mRNA to stop prematurely and a truncated protein to be produced (Figure 4). The same mutation in exone 34 of NF1 gene was found in her father.

## DISCUSSION

A very rare reason of secondary arterial hypertension in NF1 is the MAS (Criado *et al*., 2002). Our patient has characteristic signs of MAS, confirmed by angiography, ultrasonography and scintigraphy.

Renovascular hypertension is now controlled by antihypertensive medication, therefore surgical treatment was not necessary. However, this conservative therapy is

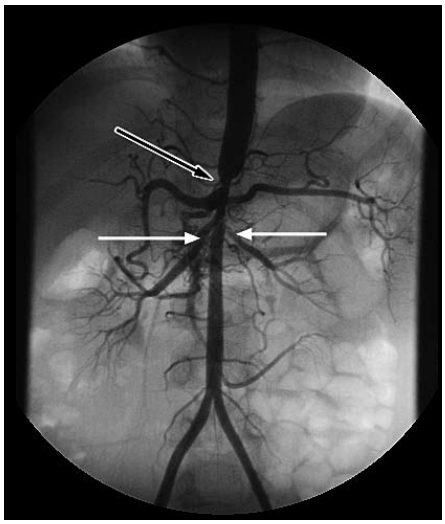

**Figure 1.** Stenosis of abdominal aorta is located near truncus coeliacus with stricture up to 3.6 mm. This narrow hypoplastic part is approximately 60 mm long (black arrow). Stenosis involvement of origin of the right renal artery, on the left side stenosis on the middle part (mid-portion) of the renal artery was noted (white arrows).

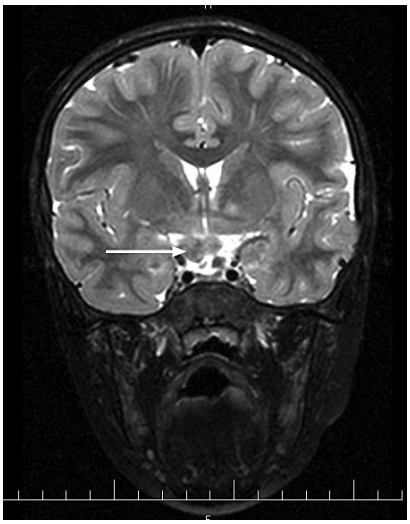

**Figure 2.** Glioma of optic chiasm (white arrow), coronal T2-TSE.F/S (T2-weighted turbo spin echo/fat saturation image).

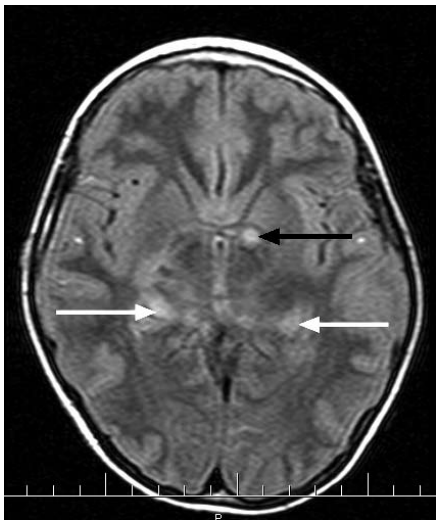

**Figure 3.** Characteristic foci of vacuolised myelin in basal ganglia (black arrow) and thalami (white arrows), axial FLAIR (Fluid attenuation inversion recovery) image.


Copyright © 2007 Neuroendocrinology Letters ISSN 0172–780X • **www.nel.edu**

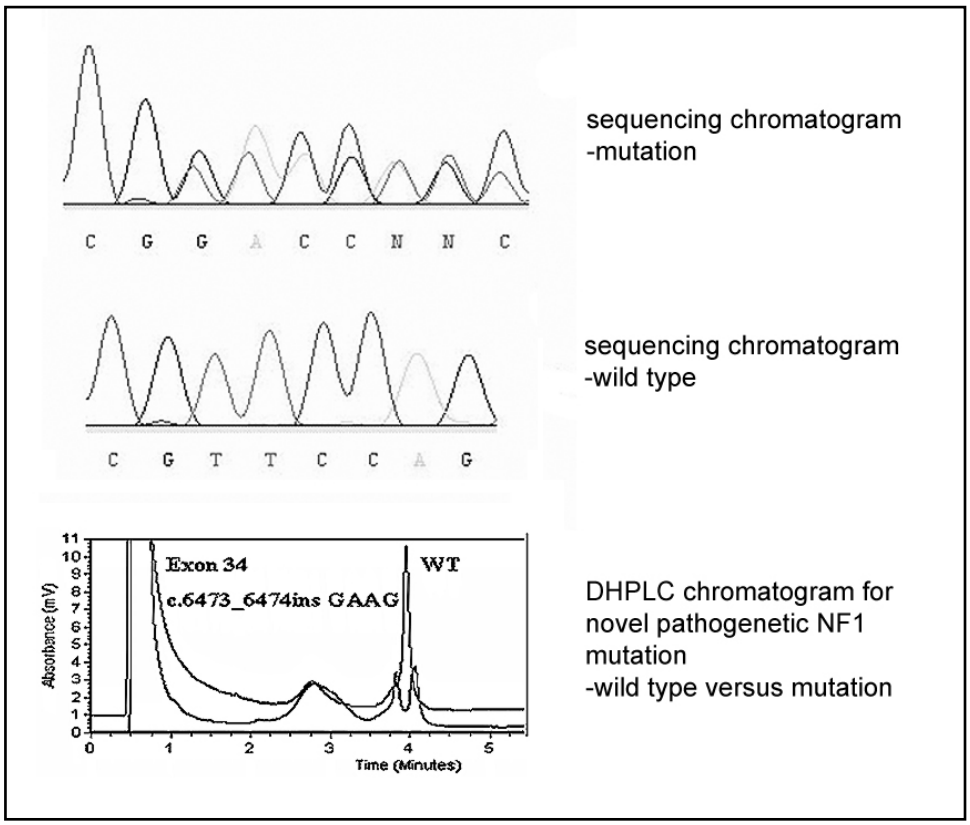


**Figure 4.** Sequencing chromatograms for NF1 mutation c.6473_6474ins GAAG (wild type and mutation). DHPLC chromatogram for novel pathogenic NF1 mutation (wild type versus mutation). This mutation was detected as change in the number of peaks.

not sufficient in many cases. Usually arterial reconstruction with introduction of bypasses and angioplasty is performed (Estepa *et al*., 2001).

Children with NF1 have neurological and oncological risks. Glioma of optic nerve is a common finding (15–20%) in patients with NF1, it is asymptomatic in 2/3 of patients. There is a long-term surveillance recommended (Listernick *et al*., 1999). In our patient, gliomas are asymptomatic, repeated cerebral MRI are without any marks of progression. Only long-term surveillance of gliomas is necessary in this case. Pubertas praecox is described in patients with NF1 and gliomas of chiasm (Habiby *et al*., 1995). Regarding the glioma of chiasm finding she has signs of the pubertas praecox and her bone age is slightly accelerated. FASI on T2-weighted MRI of the brain are typical for NF1 (Osborn & Salzman 2004). These foci are without neurological findings, but they are probably associated with development of specific learning and behaviour disabilities (at the 30–65% of children with NF1), including language development (Billingsley *et al*., 2003; Moore *et al* 1996). In our patient, there are findings of many FASI, including images in characteristic localisations. Light mental retardation and severe speech development disorder had also been found. School education is possible at the special class. Common findings in children with NF1 are scoliosis, inadequate growth and macrocephaly (Goldstein & Gutmann, 2004). Our patient possesses all of these symptoms.

NF1 is an autosomal dominant neurocutaneous disorder, with many sporadic cases.

Mutation in exone 34 of NF1 gene is novel (Bendova *et al*., in press). Also study focused on DNA analysis findings in patients with NF1 and renovascular hypertension with mid-aortic syndrome hasn't been published yet. The same mutation in exone 34 of NF1 gene was found in the father.

## CONCLUSION

NF1 is disease with multisystem involvement. Some pathological findings are signal for immediate treatment, some are just reason for a long-term surveillance.

A novel mutation in exone 34 of NF1 gene was found in our patient with NF1 and with renovascular hypertension in MAS combined with bilateral optic and chiasm glioma, speech development disorder, pubertas praecox, scoliosis and light mental retardation.

We consider the fact that her father has the same diagnosis of NF1 (including same mutation in exone 34 of NF1 gene) and that he suffered from hypertension to be very important.

## ACKNOWLEDGEMENT

This work is supported by the research grants of the Ministry of the Health Care, Czech Republic – IGA MZCR NR/7926-3, VZMZ 64203, 6503.

Ministry of Health of Czech Republic gave us permission to publish results of this research.

REFERENCES

1 Bartosh SM, Aronson AJ. 1999. Childhood hypertension. An update on etiology, diagnosis, and treatment. *Pediatr Clin North Am*, **46**, 235–252.
2 Bendova S, Krepelova A, Petrak B, Kinstova L, Musova Z, Rausova E, *et al.* 2007. Novel Mutations in the NF1 Gene in Czech Patients with Neurofibromatosis Type 1. *J Mol Neuroscience*, in press.
3 Billingsley RL, Jackson EF, Slopis JM, Swank PR, Mahankali S, Moore BD 3rd. 2003. Functional magnetic resonance imaging of phonologic processing in neurofibromatosis 1. *J Child Neurol*, **18**, 731–740.
4 Criado E, Irquierdo L, Luján S, Puras E, delMar Espino M 2002. Abdominal Aortic Coarctation, Renovascular, Hypertension, and Neurofibromatosis. *Annals of Vascular Surgery*, **16**, 363–367.
5 Delis KT, Gloviczki P. 2005. Middle aortic syndrome: from presentation to contemporary open surgical and endovascular treatment. *Perspect Vasc Surg Endovasc Ther*, **17**, 187–203.
6 Estepa R, Gallego N, Orte L, Puras E, Aracil E, Ortuno J. 2001. Renovascular hypertension in children. *Scand J Urol Nephrol*, 388–392.
7 Goldstein J, Gutmann D. 2004. Neurofibromatosis type 1. In: Roach ES, MillerVS, editors. *Neurocutaneous Disorders*. Cambridge University Press,U.K. p.42–49.
8 Habiby R, Silverman B, Listernick R, Charrow J. 1995. Precocious puberty in children with neurofibromatosis type 1. *J Pediatr*, **126**, 364–367.
9 Han SS, Cooper DN, Upadhyaya MN. 2001. Evaluation of denaturing high performance liquid chromatography (DHPLC) for the mutational analysis of the neurofibromatosis type 1 (NF1) gene. *Hum Genet*, **109**, 487–97.
10 Listernick R, Charrow J, Gutmann DH. 1999. Intracranial gliomas in neurofibromatosis type 1. *Am J Med Genet*, **89**, 38–44.
11 Moore BD3rd, Slopis JM, Schomer D, Jackson EF, Levy BM. 1996. Neuropsychological significance of areas of high signal intensity on brain MRIs of children with neurofibromatosis. *Neurology*, **46**, 1660–1668.
12 Osborn A, Salzman SK, editors 2004. *Diagnostic Imaging: Brain*. Philadelphia: Hardcover. p.78–81.
13 diPaolo DP, Zimmerman RA, Rorke LB, Zackai EH, Bilaniuk LT, Yachnis AT. 1995. Neurofibromatosis type 1: Pathologic Substrate of High-Signal-Intensity Foci in the Brain. *Radiology*, **195**, 721–724.
14 Wimmer K, Yao S, Claes K, Kehrer-Sawatzki H, Tinschert S, De Raedt T, *et al.* 2006. Spectrum of single- and multiexon NF1 copy number changes in a cohort of 1.100 unselected NF1 patients. *Genes Chromosomes Cancer*, **45**, 265–76.


Copyright © 2007 Neuroendocrinology Letters ISSN 0172–780X • **www.nel.edu**