Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Original research article

Circle of Willis abnormalities in children with neurofibromatosis type 1

Monika Bekiesińska-Figatowska *, *Hanna Brągoszewska*, *Marek Duczkowski*, *Anna Romaniuk-Doroszewska*, *Sylwia Szkudlińska-Pawlak*, *Agnieszka Duczkowska*, *Jarosław Mądzik*, *Barbara Kowalska*, *Paweł Pęczkowski*

Department of Diagnostic Imaging, Institute of Mother and Child, Warsaw, Poland

ARTICLE INFO

Article history:
Received 3 January 2013
Accepted 13 May 2013
Available online 23 January 2014

Keywords:
Neurofibromatosis type 1
Magnetic resonance angiography
Brain
Arteriopathy
Arterial variants

ABSTRACT

Background and purpose: The aim of the study was to assess anatomical variants and abnormalities in cerebral arteries on magnetic resonance angiography in 67 children with neurofibromatosis type 1 (NF1).

Materials and methods: The study included 67 children aged 9 months to 18 years (mean 6.6 years). Control group comprised 90 children aged 2–18 years (mean: 11.8 years). All patients were examined at 1.5 T scanner.

Results: We found cerebral arteriopathy (moyamoya disease) in one child (1.5%) in the study group. No aneurysms were found. Twenty-nine NF1 children (43.3%) had arterial anatomical variants. In 13 of them, more than one variant was diagnosed (44.8% of group with variants, 19.4% of study group). In control group, 19 children (21.1%) had variants, including four children with more than one variant (21% of group with variants, 4.4% of control group). Arterial variants were more common in NF1 patients compared with control group ($p = 0.026$, binomial test for two proportions). Percentage of multiple variants was higher in study group than in control group, but this difference was not significant. Variants were more frequent on left side than on the right one (significant difference in control group; $p = 0.022$, McNemara test). In study group, the number of left-sided anomalies (25) was similar to that of right-sided ones (22). There was no correlation between gender and variants, unidentified bright objects and variants or between optic gliomas and variants.

Conclusions: Occurrence of arterial variants in NF1 patients was twofold higher than in control group. Multiple variants were more frequent in the study group although the difference did not reach statistical significance. Features of cerebral arteriopathy were found in one child with NF1.

* *Corresponding author at:* Instytut Matki i Dziecka, Zakład Diagnostyki Obrazowej, ul. Kasprzaka 17a, 01-211 Warszawa, Poland.
E-mail address: m.figatowska@mp.pl (M. Bekiesińska-Figatowska).

0028-3843/$ – see front matter
http://dx.doi.org/10.1016/j.pjnns.2013.05.002

1. Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic condition caused by a mutation in, or a deletion of, the *NF1* gene located within the long arm of chromosome 17. More than 250 mutations have been identified in affected individuals. The gene product – neurofibromin – serves as a tumor suppressor. The estimated incidence of NF1 is 1:3000 [1].

Clinical diagnosis of NF1 is established in the presence of at least 2 of 7 criteria: (1) six or more *café-au-lait* spots or hyperpigmented macules greater than or equal to 5 mm in diameter in children younger than 10 years and to 15 mm in adults, (2) axillary or inguinal freckles, (3) two or more typical neurofibromas or one plexiform neurofibroma, (4) optic nerve glioma, (5) two or more iris hamartomas (Lisch nodules), (6) sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis, (7) first-degree relative with NF1 [2].

Renal artery stenosis secondary to fibromuscular dysplasia and other vascular lesions, also in the central nervous system (CNS), such as vascular ectasias, stenoses, moyamoya disease, and aneurysms, are reported more frequently in patients with NF1 than in general population [3,4]. Rarely, coronary artery aneurysms are identified in symptomatic or even asymptomatic individuals with NF1 [5].

Available literature contains mainly case reports concerning CNS vasculopathy. To our knowledge, there are only three papers based on the bigger material [6–8]. The purpose of this study is to assess the presence of anatomical variants and vascular abnormalities in cerebral arteries in children with NF1 on magnetic resonance angiography (MRA) in a group of 67 children with NF1.

2. Materials and methods

The material consisted of 67 children with NF1 diagnosed according to the above mentioned National Institute of Health Criteria Consensus Conference, aged between 9 months and 18 years (mean age 6.6 years). There were 35 boys and 32 girls in this group.

The control group consisted of 90 children aged 2–18 years, mean age 11.8 years (53 girls, 37 boys). The children included in the control group had no signs of CNS injury and were referred to magnetic resonance imaging (MRI) only because of headache.

All the children were examined at a 1.5 T scanner (GE Signa HDxt) with a 16-channel head coil. The protocol included the following sequences: SE/T1-weighted images (T1WI) in axial plane; FSPGR/3D/T1WI, sagittal; FSE/T2WI, axial, coronal; FLAIR/axial; GRE/T2*WI, axial; DWI. Children with NF1 underwent orbital magnetic resonance imaging (MRI) as well with IDEAL/T1WI, axial and FSE/T2WI + fatsat, coronal. The gadolinium-based contrast medium was administered, if necessary, in patients with NF1 in a standard dose of 0.1 mmol/kg. Magnetic resonance angiography was performed in 3D/TOF/SPGR sequence without contrast medium administration. The sequence parameters were as follows: repetition time TR = 25 ms, echo time TE = 3 ms, number of acquisitions NEX = 1, matrix MX = 384 × 224, field of view FOV = 22 × 16.5 cm, slice thickness/interslice gap ST = 1.4/−0.7 mm.

All the examinations were a part of routine clinical work-up of the patients – NF1 patients were included in the study when MRI was requested by the referring oncologist. Magnetic resonance angiography was additionally included to the routine protocol of brain MRI in children with NF1 for the purpose of this study. It made the whole examination 7 min longer. Magnetic resonance angiography was ordered by the referring neurologists as an addition to brain imaging in children included in the control group.

The institutional Bioethics Committee approval for this study was obtained. The one-sided binomial test for two proportions, McNemara two-sided significance test and Pearson correlation were used for statistical analysis of the data.

3. Results

Cerebral arteriopathy was defined as any abnormality of the intracranial arterial system that could not be considered as normal variant [7]. In the study group, one child (1.5% with 95% confidence interval [0.07%, 9.13%]) showed the signs of cerebral arteriopathy and was diagnosed as moyamoya disease (Fig. 1). We found no aneurysms in the study group and control group.

Twenty-nine children with NF1 (43.3%), 16 boys and 13 girls, turned to have arterial anatomical variants of the circle of

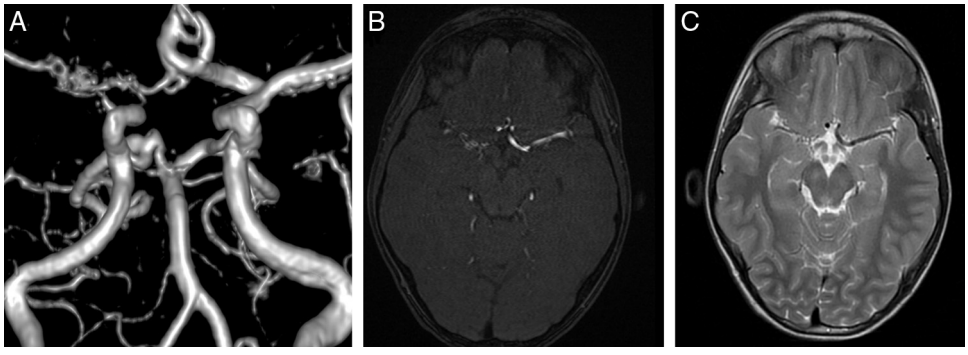

Fig. 1 – A 10-year-old boy with NF1 and stenosis/occlusion at the terminal portion of the right internal carotid artery resulting in the abnormal vascular network in the vicinity of the middle cerebral artery and anterior cerebral artery (A1). (A) MRA, VR reconstruction. (B) MRA, raw data. (C) FSE/T2WI/ax.

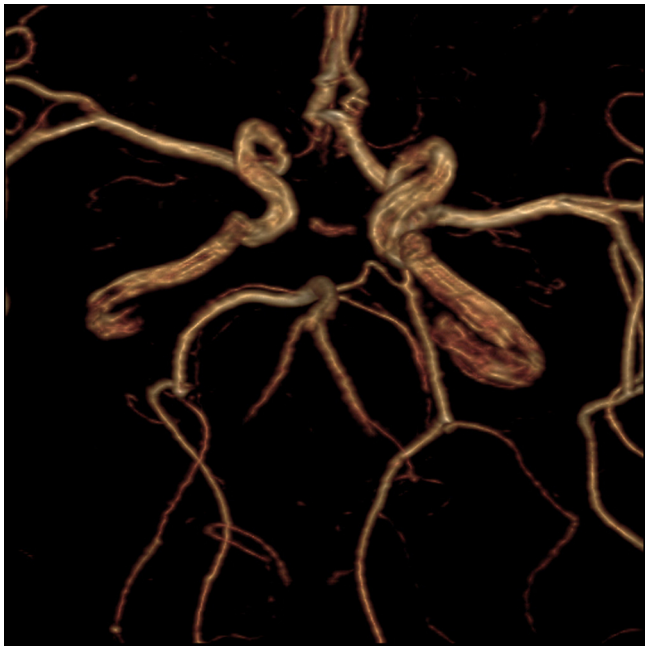

Fig. 2 – MRA. A 7-year-old boy with NF1 and right anterior cerebral artery hypoplasia in the A1 segment, right posterior communicating artery hypoplasia and left posterior cerebral artery supplied from the internal carotid artery.

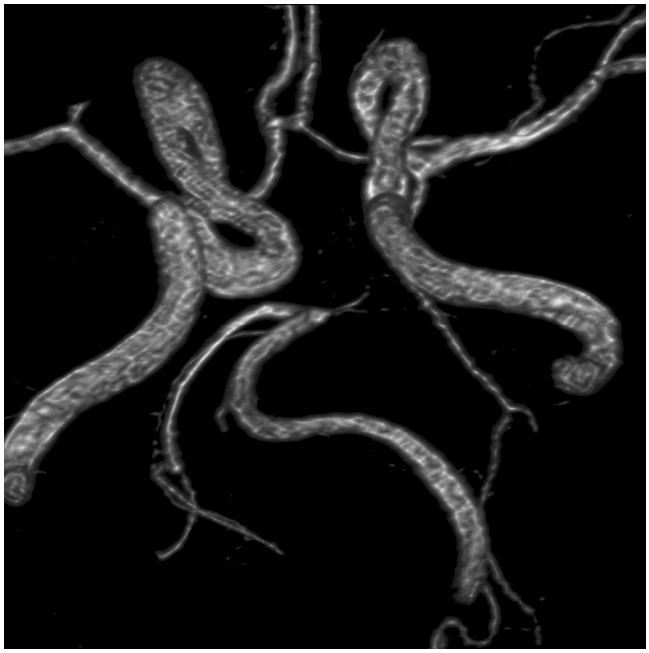

Fig. 3 – MRA. A 18-year-old boy with NF1 and right posterior communicating artery hypoplasia, kinking of right internal carotid artery, left posterior cerebral artery hypoplasia (P1) and distal posterior cerebral artery fragment supplied from the internal carotid artery. There is also hypoplasia/aplasia of the right vertebral artery.

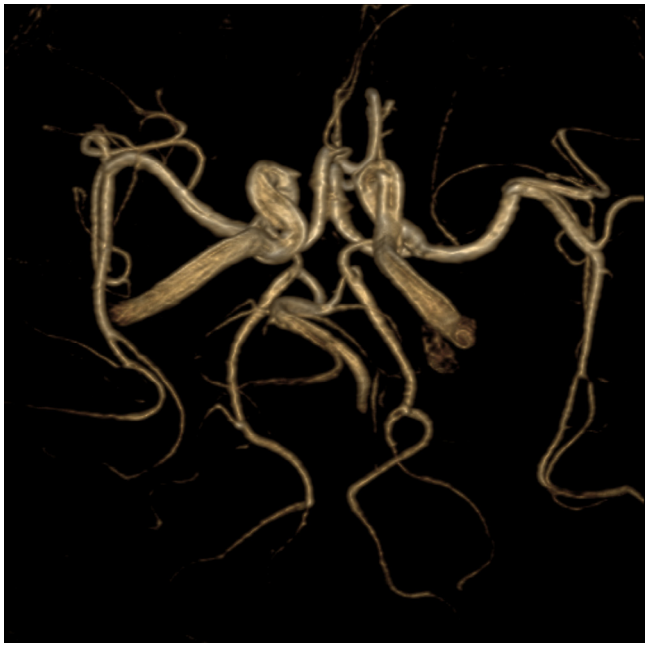

Fig. 4 – MRA. A 3-year-old boy with NF1 and bilateral kinking of internal carotid artery and posterior cerebral artery bilaterally supplied from the internal carotid artery.

Willis (Figs. 2–4). Table 1 shows diagnoses and number of cases. In 13 patients, more than one anatomical arterial variant was diagnosed (44.8% of the group with variants, 19.4% of the study group).

In the control group, 19 children (21.1%) had arterial variants (see Table 1 for details). In 4 patients from the control group, more than one variant was diagnosed (21% of the group with variants, 4.4% of the control group).

Table 1 – Arterial anatomical variants detected with magnetic resonance angiography among children with neurofibromatosis type 1 and in control group.

Aterial anatomical variants	Number of cases
Children with neurofibromatosis type 1	
Fetal configuration of circle of Willis	22
Posterior communicating artery hypoplasia	12
Kinking of internal carotid artery	6
Anterior cerebral artery hypoplasia in the proximal segment (A1)	2
Additional posterior communicating basicerebral artery	3
Hypoplasia of the posterior cerebral artery in the proximal segment (P1)	2
Hypoplasia/aplasia of the vertebral artery	1
Controls	
Posterior communicating artery hypoplasia	13
Posterior cerebral artery hypoplasia	5
Vertebral artery hypoplasia	3
Fetal configuration of circle of Willis	1
Kinking of internal carotid artery	1
Additional posterior communicating basicerebral artery	1

The presence of arterial variants was compared between the two groups by using the one-sided binomial test for two proportions. Arterial variants were more common in NF1 patients compared with those from the control group ($p = 0.026$).

Even though the percentage of multiple arterial variants was higher in the study group than in the control group, this difference did not reach statistical significance in binomial test for two proportions ($p > 0.05$).

We found vascular variants more often on the left side ($n = 17$) than on the right ($n = 8$) in the control group ($p = 0.022$, McNemara two-sided significance test). We did not observe the increased prevalence of the vascular variants on any of the sides in the study group: there were 25 variants on the left and 22 on the right. Right-sided variants were more frequent in NF1 group compared with control group ($p < 0.0001$). Left-sided variants were only a little bit more frequent in NF1 group compared with control group (one-sided $p = 0.0228$).

We also checked the correlation of the other MRI findings typical for NF1 with arterial anatomical variants. In 39 patients from the study group (58.2%), so called ''unidentified bright objects'' (UBO) were detected. Both UBO and arterial variants were observed in 19 patients – 48.7% of the patients with UBO had also arterial variants. In the remaining group of 28 patients without UBO, 12 (42.8%) showed the presence of arterial variants.

Optic gliomas were detected in 11 patients from the study group (16.4%). Arterial variants were present in three children with optic gliomas. Most of the arterial variants were observed in children without these tumors ($n = 27$).

Statistical analysis of these results was performed using Pearson correlation and two-sided significance test. Statistically significant correlation was found between the presence of UBO and optic glioma in NF1 patients ($p = 0.016$). There was no correlation between gender and presence of arterial variants, between UBO and arterial variants and between optic gliomas and arterial variants.

4. Discussion

The previous, few publications concerning cerebrovascular anomalies in children with NF1 are not comparable with our study. In the first of them, by Rosser et al. [6], brain MR examinations of 316 children were retrospectively reviewed. Eight of these patients had brain abnormalities indicating vascular pathology and these 8 patients only underwent MRA. Seven of them showed signs of cerebral arteriopathy as defined above; in the eighth patient an anatomical variant was found (hypoplastic right internal carotid artery) [6]. In the second paper, by Cairns and North [7], brain MRI was performed in 144 patients with NF1. Seven of these children underwent MRA which revealed cerebral arteriopathy (arterial stenosis or occlusion in 7 cases and moyamoya in 5). In the third paper, by Rea et al. [8], 266 patients underwent brain MRI, (35 of them – MRA). Seventeen children showed the signs of cerebral arteriopathy: two on MRI only, and 15 – on MRI and MRA. Also in that paper, anatomical vascular variants were not assessed.

The presented study was planned as a prospective one for the years 2009–2011 at the Institute of Mother and Child in Warsaw, a tertiary referral center for patients with NF1. Over this period, all NF1 patients referred to brain MRI had MRA performed as well.

Magnetic resonance angiography has been shown to be well suited to investigate the circle of Willis providing both morphological and hemodynamic information. The latter, concerning blood flow direction, is possible to obtain by means of 2D phase-contrast sequences of which one is phase encoded in the anteroposterior direction and the other in the left-right direction [9]. In our study, we did not assess flow direction and only morphological data were analyzed. Time-of-flight MRA which was applied in our study is easy to perform and does not require any contrast media, which is associated with lower costs and no adverse effects. Its main disadvantage is low sensitivity to slow and turbulent blood flow, because of intravoxel dephasing and spin saturation. However, its diagnostic performance has been proved in many previous studies [10] and its value as a screening method is well established. Its usefulness to visualize vessel patency of the circle of Willis and first order branches in children independent of age has been shown many years ago. In the beginning of its use, the time of this sequence was quite long and made the whole examination as much as even 20 min longer [11]. Currently, also in our study, the extra time needed to perform MRA was no longer that 7 min.

As stated above, one of our patients from the study group (1.5%) showed the signs of cerebral arteriopathy, defined as any abnormality of the intracranial arterial system that could not be considered as normal variant [8]. In this patient, we found stenosis/occlusion at the terminal portion of the right internal carotid artery resulting in abnormal weak signal from the right middle and anterior arteries with abnormal vascular network in the vicinity of the occlusive/stenotic area – features of moyamoya disease (Fig. 1a–c). They were not accompanied by the ''ivy'' sign on FLAIR images although lack of normal flow void of middle cerebral artery and A1 and flow voids of abnormal tiny vessels were observed on FLAIR and T2-weighted images (Fig. 1c). The reported prevalence of cerebrovascular abnormalities in NF1 children in the literature is higher: from 2.5% [5] up to 6% [8]. In the latter, it is even stated that this number (6%) is likely an underestimate. As mentioned above, only a part of these patients underwent MRA. To our knowledge, our study is the first prospective one assessing the prevalence of cerebral vasculopathy in NF1 children with MRA and our results do not confirm such high estimates. This is an important finding as childhood arteriopathy implies the risk of early stroke as a complication and may require antiplatelet therapy to lower the risk of neurological sequelae or even surgical intervention [8]. Cerebral vasculopathy, if present, can produce serious complications and contribute to mortality at younger ages [12].

Instead, we found high frequency of anatomical arterial variants in the study group which were present in as many as 43.3% of the patients with NF1. Almost in half of this subgroup (44.8%) MRA revealed multiple anatomical variants (Figs. 2–4). We did not find the reports in the literature concerning the prevalence of these variants in NF1 population, only case reports [13,14].

The definitions of circle of Willis variants have been described in previous publications [9,15]. The fetal configuration of circle of Willis is defined as P1 smaller than posterior

communicating artery with ipsilateral P2 supplied by internal carotid artery via posterior communicating artery [15]. Hypoplasia or absence of the arteries is also considered as anatomic variations with hypoplasia defined as vessel diameter smaller than 0.8 mm [9]. In pathological literature, hypoplastic vessels are defined as having external diameter smaller than 1 mm [16]. There are also publications in which the assessment of vessels' diameters is based on visual inspection: A1 hypoplasia is diagnosed when the artery is assessed as very thin and showing a great difference from the contralateral one, and P1 hypoplasia - when its diameter is assessed as clearly smaller than that of posterior communicating artery at the junction [17]. In our study, visual inspection according to the above mentioned criteria was the basis of the observations. Tortuosity, kinking or coiling are also included in the morphological variations of internal carotid artery, although they can be acquired as well. They are found in infants and even in fetuses, and are thought to be congenital, frequently ascribed to embryological causes [18,19]. Internal carotid artery is formed from the third aortic arch and dorsal aorta so in the embryo it is normally kinked. The vessel straightens when the fetal heart and large vessels recede in the thoracic cavity. If the embryological state persists, it produces undulations, loops, and kinks [20].

During the same period, we examined a group of 90 children who had no signs of CNS injury and suffered from headaches. These children constituted the control group in which the frequency of anatomical arterial variants was significantly lower (21.1%). Multiple variants were detected in 21% of this subgroup; those variants were rarer, but the difference of frequency of multiple variants between the study and control groups did not reach statistical significance. Koelfen et al. [11] in their study of 140 children demonstrated anatomic variations in 15% of patients on MRA.

Posterior cerebral artery originating from the internal carotid artery was found the most often in our study group (Figs. 2–4). In an MRA study of 100 healthy individuals, this variant was found in 13% [21].

Posterior communicating artery hypoplasia was the second most frequent anomaly in the study group (Figs. 2–3) and the first one in the control group. This is in accordance with the existing literature: in the above mentioned paper it was noted in as many as 21% of the healthy subjects [21]. In the autopsy study of 1 000 brains, posterior communicating artery was absent in 1% and hypoplastic in 13.2% while the anterior communicating artery was absent in 1.8% [22]. No abnormalities of anterior communicating artery were found in our material.

The arterial variants revealed by MRA in our patients were not life-threatening and did not require any treatment. Nevertheless, the normal arrangement of the circle of Willis is of high physiologic significance. If one of the arteries supplying the circle of Willis or one part of the circle is hypoplastic, stenosed or occluded, blood flow from the other vessels can often preserve the cerebral perfusion well enough to avoid ischemia. The main role in this aspect is attributed to the anterior communicating artery, posterior communicating artery is considered as less important [23].

We did not observe the increased prevalence of the arterial variants on any of the sides in NF1 children. As opposed to the findings of Macchi et al. [21] who found that anomalies (in general population) occurred more commonly on the left than on the right side, we showed 25 variants on the left and 22 on the right in our study group. However, in the control group our results were similar to those of the above mentioned authors: there were 17 anatomical arterial variants on the left side versus 8 on the right. Interestingly, the arterial variants in NF1 patients in our material were more frequent on the right side as compared to the control group and general population.

In some papers, statistically significant correlation has been found between anatomical variations of anterior cerebral artery, posterior cerebral artery and posterior communicating artery and development of anterior communicating artery and internal carotid artery aneurysms [17]. Thus, the increased incidence of arterial variants shown in our material may be associated with increased risk of aneurysms formation in NF1 patients described by other authors.

5. Conclusions

1. The occurrence of arterial anatomical variants in NF1 patients was twofold higher than in general population which was statistically significant.
2. In the study group multiple anatomical variants were more frequent than in the control group although the difference did not reach statistical significance.
3. The prevalence of cerebral arteriopathy in children with NF1 was 1.5% in our material which is rarer than estimated in other, few papers.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

[1] Zajączek S. Nerwiakowłókniakowatość typu 1 (NF1, choroba v Recklinghausena). In: Lubiński J, editor. Nowotwory dziedziczne 2002. Profilaktyka, diagnostyka, leczenie. Poznań: Termedia; 2003. p. 129–34.
[2] Jastrzębska M, Bekiesińska-Figatowska M, Karwacki M, Iwanowska B, Uliasz M. MR imaging features in children

with type 1 neurofibromatosis (NF1): intra- and extracranial lesions. Pol J Radiol 2009;74:14–21.
[3] Srinivasan A, Krishnamurthy G, Fontalvo-Herazo L, Nijs E, Meyers K, Kaplan B, et al. Spectrum of renal findings in pediatric fibromuscular dysplasia and neurofibromatosis type 1. Pediatr Radiol 2011;41:308–16.
[4] Oderich GS, Sullivan TM, Bower TC, Gloviczki P, Miller DV, Babovic-Vuksanovic D, et al. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. J Vasc Surg 2007;46:475–84.
[5] Smith A, Araoz PA, Kirsch J. Coronary arterial aneurysms in neurofibromatosis 1: case report and review of the literature. J Thorac Imaging 2009;24:129–31.
[6] Rosser TL, Vezina G, Packer RJ. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology 2005;64:553–5.
[7] Cairns AG, North KN. Cerebrovascular dysplasia in neurofibromatosis type 1. J Neurol Neurosurg Psychiatry 2008;79:1165–70.
[8] Rea D, Brandsema JF, Armstrong D, Parkin PC, deVeber G, MacGregor D, et al. Cerebral arteriopathy in children with neurofibromatosis type 1. Pediatrics 2009;124:e476–83.
[9] Hartkamp MJ, van Der Grond J, van Everdingen KJ, Hillen B, Mali WP. Circle of Willis collateral flow investigated by magnetic resonance angiography. Stroke 1999;30:2671–8.
[10] Serafin Z, Strześniewski P, Lasek W, Beuth W. Methods and time schedule for follow-up of intracranial aneurysms treated with endovascular embolization: a systematic review. Neurol Neurochir Pol 2011;45:421–30.
[11] Koelfen W, Wentz U, Freund M, Schultze C. Magnetic resonance angiography in 140 neuropediatric patients. Pediatr Neurol 1995;12:31–8.
[12] Tang SC, Lee MJ, Jeng JS, Yip PK. Novel mutation of neurofibromatosis type 1 in a patient with cerebral vasculopathy and fatal ischemic stroke. J Neurol Sci 2006;243:53–5.
[13] Klaus E, Nekula J, Minarikova E, Fárková H. Von Recklinghausen's neurofibromatosis with intracranial stenosis of the internal carotid artery and orbito-sphenoidal bone dysplasia. Rofo 1978;129:250–2.
[14] Ohta H, Hashimoto M, Urasaki E, Yokota A. Hypoplasia of internal carotid artery at cervical portion associated with neurofibromatosis type I. No To Shinkei 2002;54:1003–6.
[15] van der Grond J, van Raamt AF, van der Graaf Y, Mali WP, Bisschops RH. A fetal circle of Willis is associated with a decreased deep white matter lesion load. Neurology 2004;63:1452–6.
[16] Eftekhar B, Dadmehr M, Ansari S, Ghodsi M, Nazparvar B, Ketabchi E. Are the distributions of variations of circle of Willis different in different populations? - results of an anatomical study and review of literature. BMC Neurol 2006;6:22.
[17] Horikoshi T, Akiyama I, Yamagata Z, Sugita M, Nukui H. Magnetic resonance angiographic evidence of sex-linked variations in the circle of Willis and the occurrence of cerebral aneurysms. J Neurosurg 2002;96:697–703.
[18] Sacco S, Totaro R, Baldassarre M, Carolei A. Morphological variations of the internal carotid artery: prevalence, characteristics and association with cerebrovascular disease. Int J Angiol 2007;16:59–61.
[19] Ovchinnikov NA, Rao RT, Rao SR. Unilateral congenital elongation of the cervical part of the internal carotid artery with kinking and looping: two case reports and review of the literature. Head Face Med 2007;3:29.
[20] Desai B, Toole JF. Kinks, coils, and carotids: a review. Stroke 1975;6:649–53.
[21] Macchi C, Catini C, Federico C, Gulisano M, Pacini P, Cecchi F, et al. Magnetic resonance angiographic evaluation of circulus arteriosus cerebri (circle of Willis): a morphologic study in 100 human healthy subjects. Ital J Anat Embryol 1996;101:115–23.
[22] Kapoor K, Singh B, Dewan LI. Variations in the configuration of the circle of Willis. Anat Sci Int 2008;83:96–106.
[23] de Boorder MJ, van der Grond J, van Dongen AJ, Jaap Kappelle L, Van Rijk PP, Hendrikse J. SPECT measurements of regional cerebral perfusion and carbon dioxide reactivity: correlation with cerebral collaterals in internal carotid artery occlusive disease. J Neurol 2006;253:1285–91.