

Progressive Unilateral Hemispheric Atrophy in an Infant with Neurofibromatosis

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Key words

- Neurofibromatosis
- brain
- hemispheric atrophy
- buphthalmos
- vasculopathy
- hemispherotomy

Abstract



Introduction: Cerebrovascular diseases are rarely seen in neurofibromatosis type 1. These include vascular occlusive disease, moyamoya vessels, aneurysms, arteriovenous malformations and fistulae.

Case Report: We describe the case of an infant with genetically proven neurofibromatosis type 1 and progressive brain hemiatrophy over months, due to primary narrowing of intracranial carotid

artery branches, as demonstrated by successive brain imaging. She presented with refractory seizures and a progressive hemiparesis associated with developmental delay. Surgical material from hemispherotomy done at 18 months showed severe abnormalities of the small vessels.

Conclusion: Cerebrovascular changes seen in neurofibromatosis can be diffuse and progressive, with secondary hemiparesis, epilepsy and developmental delay.

Abbreviations



MRA	MR angiogram
MRI	magnetic resonance imaging
NF1	neurofibromatosis type 1

Introduction



Von Recklinghausen's disease (neurofibromatosis type 1, NF1) is a genetic disorder caused by a mutation in the NF1 gene on chromosome 17 and includes a broad spectrum of clinical manifestations due to dysplasia of mesodermal and neuroectodermal tissues. NF1 vasculopathy, first reported in 1945 by Reubi [13], is a potentially serious but less known manifestation of this multisystem disorder, affecting arterial and venous blood vessels of all sizes. Vascular changes (including stenosis, occlusions, aneurysms, or arteriovenous fistulae) may occur in the entire arterial tree from the proximal aorta to the small arteries, but these changes are most commonly seen in the renal arteries, the aorta, the mesenteric and rarely in the cerebral arteries [1, 4, 7]. Several cases of cerebrovascular NF1 have been reported in the literature [14, 17], showing vascular occlusive disease, moyamoya vessels, aneurysms, arteriovenous malformations and fistulae.

However, to our knowledge, there are only a few case reports documenting brain hemiatrophy associated with NF1 vasculopathy, and progression and neuropathology were never mentioned [3, 8, 12]. We describe here the progression of the imaging patterns of one young child developing hemispheric brain atrophy related to NF1 vasculopathy, and the corresponding pathological findings.

Case Report



This girl's medical history began at birth with the discovery of a right buphthalmos with glaucoma and macrocephaly (36.5 cm). She was the first child of non-consanguineous healthy parents. Family history was negative for epilepsy or neurological disease, and particularly NF1. Pregnancy and delivery at term were uneventful. Physical and neurological examinations were normal except for a small capillary hemangioma on the nose. Ocular examination displayed right corneal opacity, irian neovessels, and a pale and hemorrhagic retina.

She was admitted at 15 days, because of suspected epileptic seizures (abnormal ocular movements, pallor, cyanosis, chewing, hypotonia and apnea), with relapse at one month. At this time,

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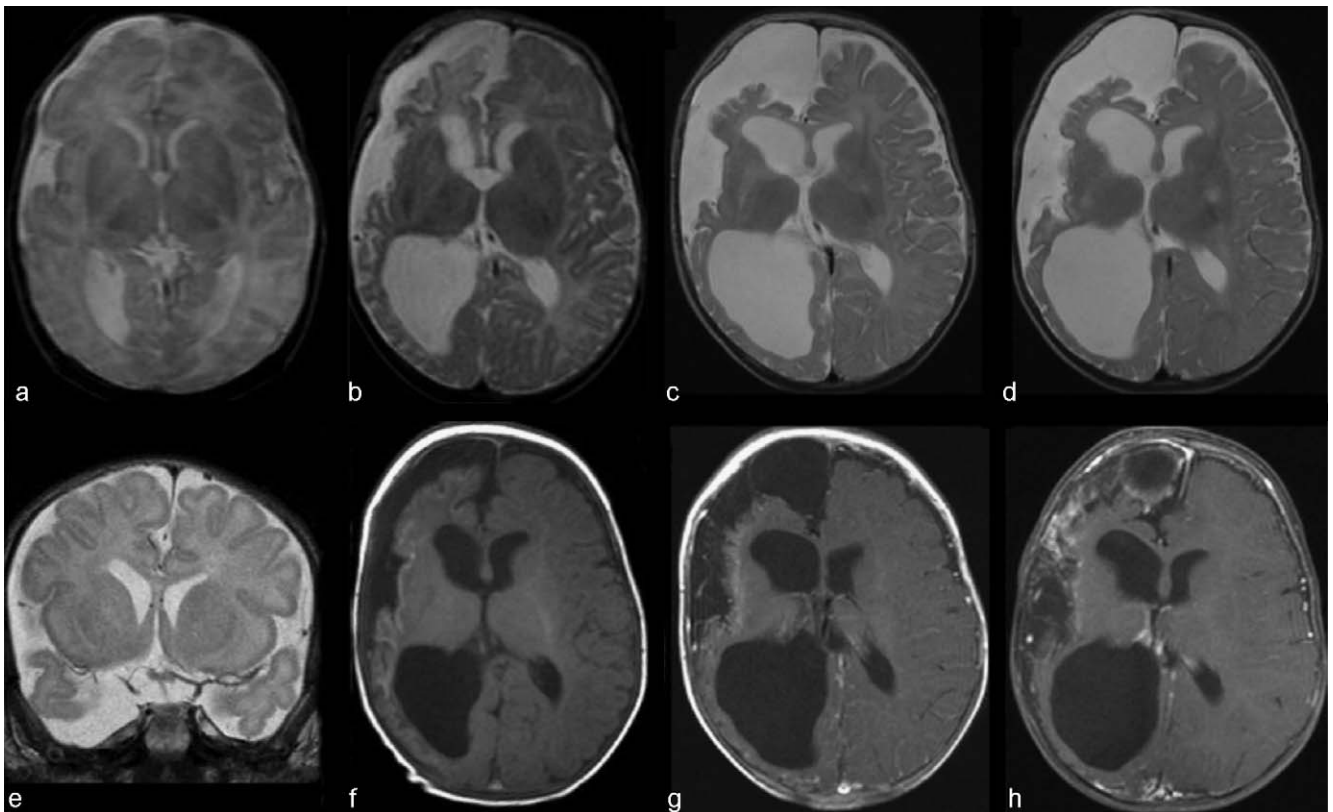


Fig. 1 Transverse T₂-weighted MRI at age of 20 days (a), 3 months (b), 6 months (c) and 1 year (d) showing progressive atrophy of the right cerebral hemisphere with concomitant ventricular dilatation. Coronal T₂-weighted MRI at age of 20 days showing narrowed internal carotid artery, middle cerebral artery, and anterior cerebral artery on the right side and speaking for primary disease of the large vessels (e). Transverse T₁-weighted MRI after gadolinium injection at age of 3 months (f), 6 months (g) and 1 year (h) showing development of pial collateral vascularization on the right hemisphere.

numerous café-au-lait spots with a diameter larger than 0.5 cm were noted. The nasal angioma had disappeared. Phenobarbital was started. Neurofibromatosis type 1 was clinically diagnosed. The epilepsy rapidly worsened despite the many treatments attempted. At 2.5 months she had numerous partial seizures, with progressive left hemiparesis and developmental regression (loss of social smile, ocular fixation and vocalization). At 3 months the glaucoma could no longer be controlled medically and enucleation of the right eye was performed.

Infantile spasms appeared at 5 months. At 12 months the child was normocephalic (46.5 cm) with a wide fontanel. Axial hypotonia, left hemiparesis, left hemianopsia, and severe developmental delay (estimated at a level of 4 months) were noted. Seizures were almost continuous and completely refractory to polytherapy. At 18 months, she underwent a right peri-insular hemispherotomy, consisting in disconnecting the hemisphere through minimal brain resection [19]. The initial postoperative period was uneventful without any seizure or new neurological deficit. Four weeks later, the child developed hydrocephalus that required a ventriculoperitoneal shunt. She had no further complications.

At present, she is 5.5 years old and seizure-free since surgery with a low dose of valproic acid. She is normocephalic (51 cm), with a left-sided hemianopsia of the remaining left eye, and an important developmental delay. She is, however, able to interact with her family, to use her residual vision to catch objects, and to move around by shuffling.

DNA analyses demonstrated a mutation in the neurofibromin gene (p.L194P) that was not found in the parents.

EEG findings

Initial EEG recordings between age 3 weeks and 2 months showed a right asymmetry of the background activity with a relative slowing and electrical and/or subtle seizures intermittently in the central-temporal region. From 3 months, the asymmetry increased with a very monotonous low voltage activity on the right hemisphere associated with focal stereotyped epileptiform complexes in the occipital region. Independent central-parietal-occipital epileptic activity appeared on the left hemisphere. At 5 months infantile spasms were recorded and a hypersarrhythmic pattern was seen on the left side only. The activity on the right hemisphere remained abnormally monotonous and of low voltage. This pattern persisted until hemispherotomy.

In the last recording at 5 years 4 months (four years after surgery), no more epileptic activity was recorded. A slight slowing was observed on the left hemisphere, and a very monotonous activity of low voltage was seen on the right hemisphere.

Radiological findings (• Figs. 1, 2)

The first magnetic resonance imaging (MRI) at 20 days (• Fig. 1a) showed mild enlargement of the right lateral ventricle, and a temporal arachnoid cyst; the cortex and the white matter were normal. The internal carotid artery, middle cerebral artery, and anterior cerebral artery on the right side were already smaller than those on the left, speaking for primary disease of the large vessels (• Fig. 1e).

MRI at 3 months (• Fig. 1b) showed diffuse right hemispheric atrophy with increased right lateral ventricle enlargement, and widening of the right pericerebral space. MRI at 6 months

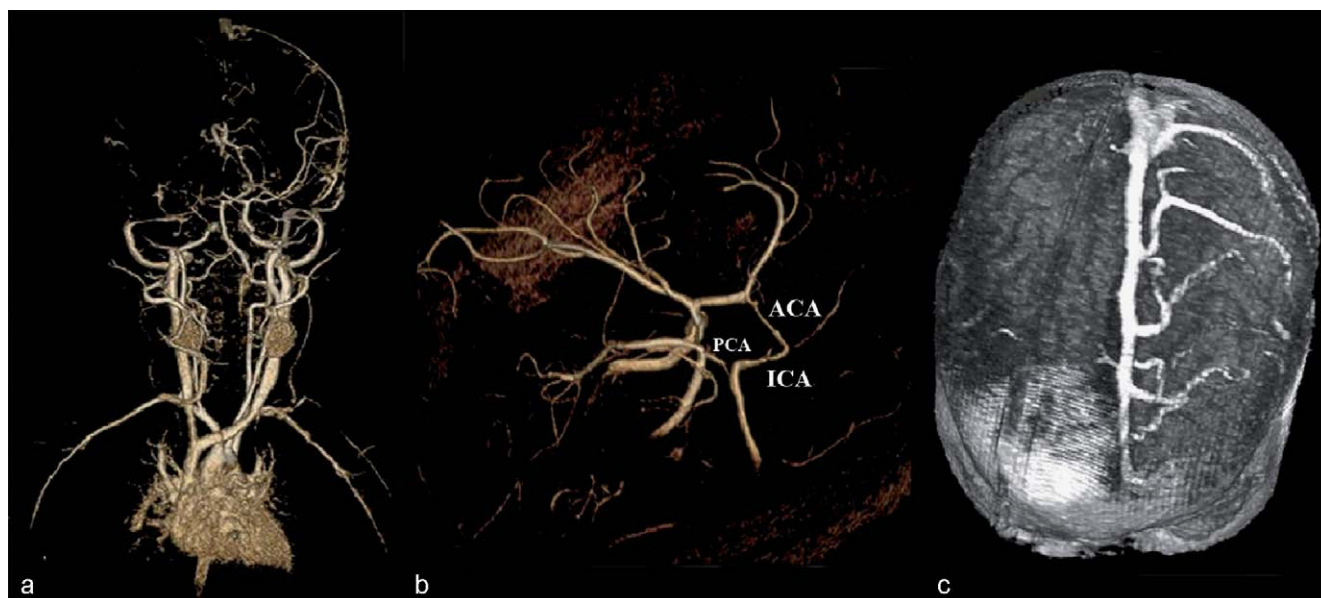


Fig. 2 (a) 3D reconstruction of contrast MRA at age of 1 year showing a global view of the neck and intracranial vessels. The flow in the intracranial ICA and its branches is almost absent on the right side as well as the cortical veins. (b) 3D reconstruction of intracranial TOF arterial MRA showing very narrowed internal carotid artery, anterior cerebral artery, and posterior cerebral artery and absent middle cerebral artery on the right side. (c) 3D reconstruction of TOF venous MRA showing the absence of cortical veins on the right hemisphere.

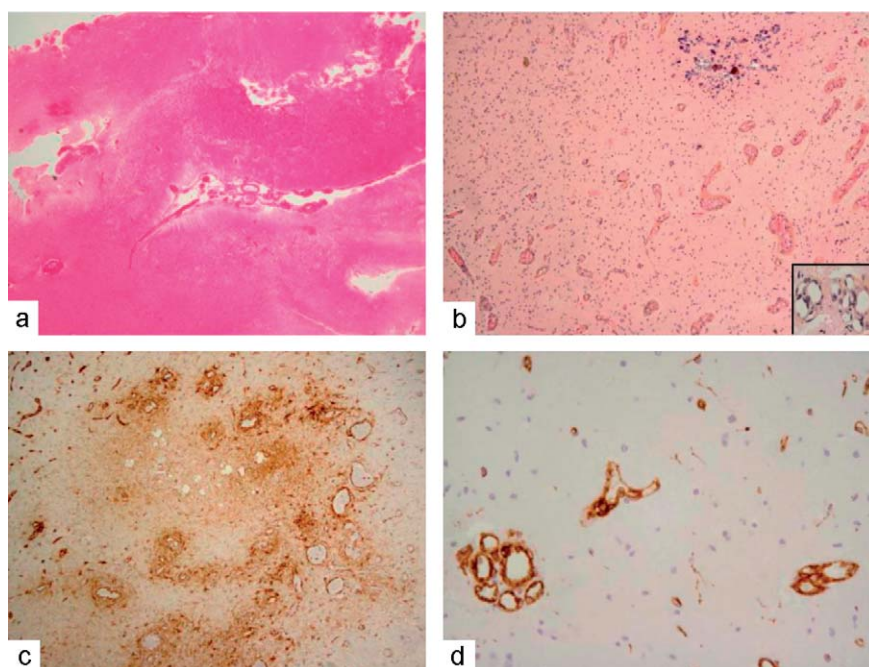


Fig. 3 (a) Severe atrophy of cerebral cortex and underneath white matter with increased density within the cortex (H&E $\times 20$). (b) Prominent vessels walls within the cerebral cortex with increased collagen fibers within the walls (HPS $\times 200$). (c) Immunohistochemistry with GFAP revealing intense positivity of glial cell fibers surrounding the abnormal vessel walls ($\times 200$). (d) Immunohistochemistry with SMA revealing positivity of small vessels walls for smooth muscle fibers ($\times 200$).

(**Fig. 1c**) and at 12 months (**Fig. 1d**) displayed further right hemiatrophy and right parieto-occipital enhancement after gadolinium injection, suggesting leptomeningeal collaterals (**Figs. 1f–h**). No dilated collaterals were seen in the basal cisterns. Although brain shrinkage was the most prominent phenomenon, there was also a slight increase of the white matter signal on T_2 -weighted images, particularly in the frontal region, presumably representing gliosis. The right choroid plexus was slightly increased. There was no abnormality on the other side. An MR angiogram (MRA) at 12 months displayed normal anatomy of the circle of Willis, and persisting severely decreased flow in the right internal carotid (from the carotid siphon), anterior, middle and posterior cerebral arteries (**Figs. 2a, b**). The

venous study showed a striking absence of visible cortical veins on the right side (**Fig. 2c**).

Areas of increased T_2 signal typical of abnormal myelination seen in NF1 became visible in the cerebellum in the 2nd and 3rd years of life (not shown).

Pathological findings (**Fig. 3**)

Review of material from the right eye lesions revealed a large irian hamartoma and a plexiform neurofibroma of the ciliary nerve. Underneath these lesions, a cluster of small vessels, capillaries and arterioles was seen, with small lumina due to thick endothelial lining and proliferation of smooth muscle fibers. These vessels were reminiscent of glomeruloid structures.

A small amount of tissue was received from the material removed at time of the peri-insular hemispherotomy. It consisted of fragments of hippocampus, cerebral amygdala, cerebral cortex and white matter from the temporal lobe. All this material revealed severe changes of atrophy in which numerous abnormal looking and prominent vessels were seen as well as a significant astrogliosis. These vessels, capillaries, arterioles or veinules had thickened walls bordered by endothelial cells, reticulin fibers and some smooth muscle cells. Their walls also appeared to be thickened by the apposition of numerous foot processes arising from the increased astrocytic component surrounding them. The rare remaining neurons showed no dysplastic changes.

Discussion

Our patient with genetically proven NF1 presented a documented progressive right cerebral hemiatrophy, which occurred within months. The clinical course with progressive hemiparesis and epilepsy, as well as the data of the successive brain imaging and the neuropathology suggested a progressive ischemic damage due to a diffuse cerebral vasculopathy, affecting large and small cerebral vessels. A thinning of the intracranial portion of the internal carotid artery was already present in the first MRI at age of 20 days and the MRA at age of 1 year showed decreased flow in the right internal carotid already at the level of the carotid siphon. The location of this vasculopathy was in accordance with previous studies, which reported that the internal carotid artery was most frequently involved, usually at the supraclinoid level, with middle cerebral artery, anterior cerebral artery, and posterior cerebral artery being involved with decreasing frequency [14]. An abnormal collateral leptomeningeal vascular network developed progressively, affecting the entire hemisphere, related to chronic ischemia. Neither the successive MRI nor the MRA showed apparition of collateral circulation in the basal ganglia, also called secondary moyamoya phenomenon, as sometimes reported in patients with NF1 [5]. The few published reports of focal brain atrophy in NF1 describe the end-stage but not the progression of this pathology over time [3,8,12]. Dubois et al. in 1951 [3] presented a 39-year-old female patient with diagnosed NF1 and with severe developmental delay that they related to a cerebral atrophy. Kuwayama et al. in 1985 [8] described a 16-year-old male patient with diagnosed NF1 who developed seizures and left hemiparesis related to atrophy of the right hemisphere and occlusion of the right internal carotid artery. Pistorius et al. in 1994 [12] reported the case of another 39-year-old female patient with diagnosed NF1 and with a right hemiplegia related to a left hemispheric atrophy, predominant in the temporoparietal region. Early epilepsy was the first clinical manifestation in our case. The prevalence of seizures in NF1 has been reported to range from 3.8–7%, this risk being mainly related to intracranial masses and cortical malformations [20] that were not found in our case. Because of the nearly continuous and refractory seizures, we first thought that the atrophy was secondary to the epileptic process, by analogy with the hemiconvulsion-hemiplegia-epilepsy syndrome [15]. However, the marked vascular abnormalities found in the large and the smaller cerebral vessels by MRA and neuropathology did not fit in with the normal angiographic findings and the cortical laminar necrosis reported in this syndrome [15, 18]. Neither did they fit with the neuropathological findings from hemispherectomies in children [2]. We also

thought of a mixed neurocutaneous syndrome, some MRI features (leptomeningeal collaterals, and enlargement of the choroid plexus) suggesting Sturge-Weber syndrome, in which unilateral cerebral atrophy is suspected to result from a vascular (absence of the normal cortical venous drainage) or epileptic process [6]. It is striking that in Sturge-Weber syndrome cerebral imaging findings are also often reported as being normal in the neonatal period, the leptomeningeal vascular dysplasia becoming progressively more apparent with time and ipsilateral hemiatrophy developing slowly as a secondary feature. A PHACE or Pascual-Castroviejo type II syndrome [9–11] could have been another explanation for progressive occlusion of cerebral arteries, but has been discarded for the two following reasons. First, the small nasal hemangioma noted at birth disappeared completely after 2 weeks (confirmed by two dermatological exams in the first year of life). Second, the MRA showed no persistent embryonic arteries in association with the narrowing of internal carotid artery described in this syndrome.

Another interesting feature was the congenital buphthalmos, which is a rare manifestation of NF1. It has been suggested that the pathogenesis for glaucoma is obstruction of the aqueous humor outflow channels by the presence of an intraocular mass [16]. In this case, the glaucoma could also originate from modification of endothelial cells and smooth muscle cells of the corneoscleral meshwork of the aqueous humor outflow channels by the loss of neurofibromin expression. Detection of neurofibromin expression in these cells would be a hypothesis to investigate. In our case, the glaucoma and the hemiatrophy were both right-sided. This raises the question of a particular vulnerability of one side in an individual to loss of neurofibromin expression (asymmetric gene expression?). Facial or body asymmetry is reported in NF1, making this question of particular interest.

Conclusion

This case shows clearly that cerebral vascular changes seen in neurofibromatosis can be progressive and diffuse, with brain atrophy and epilepsy. Vessels in the enucleated eye were already pathologically thickened, before cerebral atrophy became clearly obvious. Brain hemiatrophy appeared progressively but relatively quickly, over months. Cerebrovascular changes in neurofibromatosis not only cause acute strokes, but also induce progressive clinical manifestations like seizures, hemiparesis, and developmental delay. In cases of pharmacologically refractory seizures, surgical treatment of epilepsy should be considered.

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