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Brainstem ischemic syndrome in juvenile NF2

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Abstract

Objective

A new case of brainstem ischemic necrosis in a young woman with de novo neurofibromatosis type 2 (NF2) is reported, and given notable similarities to 7 prior cases of brainstem stroke in the literature, features defining a possible syndrome were sought.

Methods

Case review including detailed clinical assessment, neuroimaging analysis, genetic testing, and brain biopsy, followed by a multicase analysis.

Results

Brainstem ischemia in juvenile NF2 typically occurs in teenagers without previously known NF2 as an acute, monophasic presentation with restricted diffusion in the midbrain or pons following a recent hypoperfusion event, normal vascular imaging, obvious intracranial imaging features of NF2, typical inactivating *NF2* alterations, biopsy showing necrosis without small vessel pathology, and subsequent aggressive NF2 lesion progression.

Conclusions

Brainstem ischemia in juvenile NF2 is a rare syndrome of unclear etiology, possibly reflecting an unknown underlying vascular abnormality; a digenic effect is not excluded.

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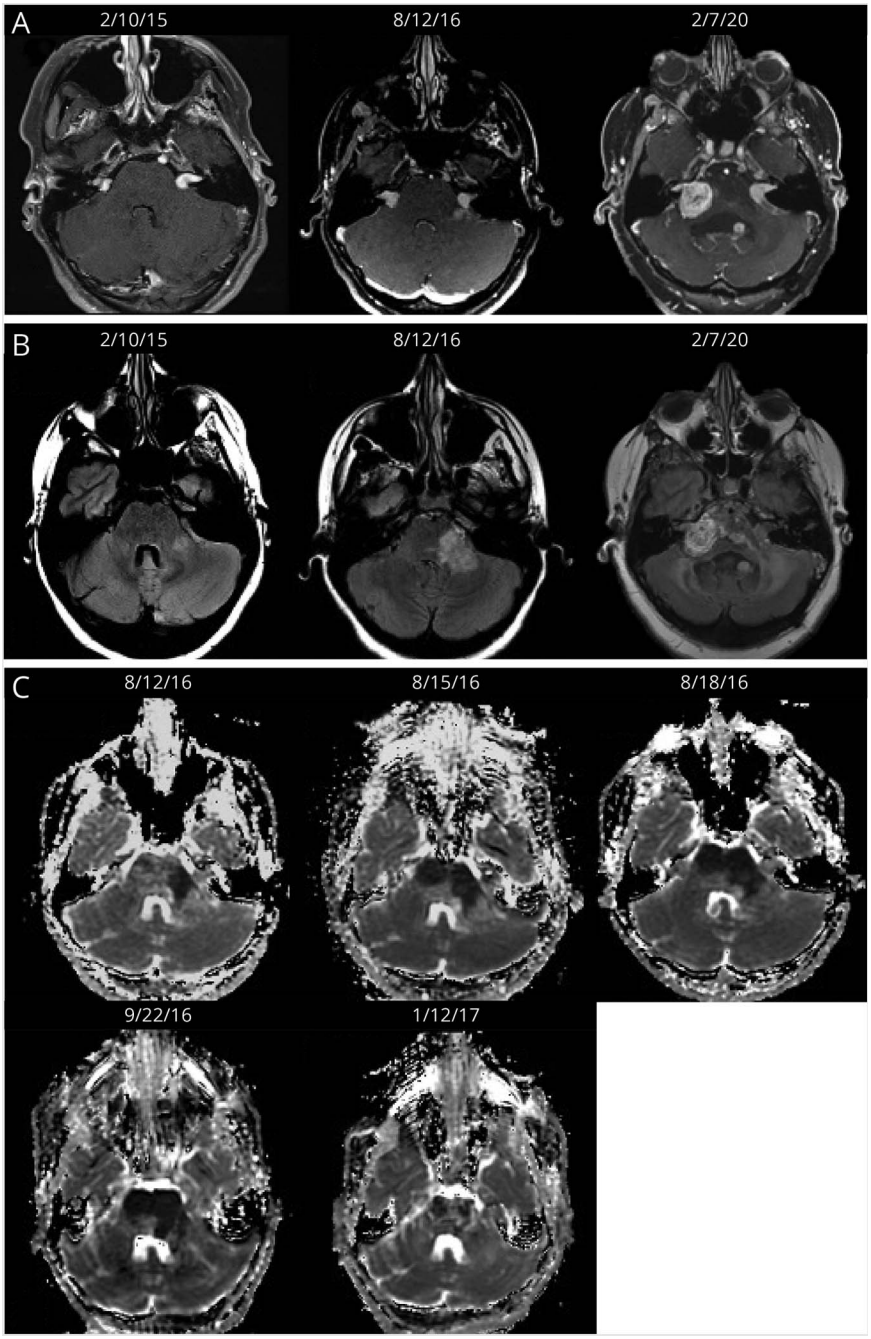
GLOSSARY

ADC = apparent diffusion coefficient; **CPM** = central pontine myelinolysis; **NF2** = neurofibromatosis type 2.

Neurofibromatosis type 2 (NF2) usually presents in patients in their early 20s with symptoms related to vestibular schwannomas. Younger age at onset occurs in nearly 20% of patients with NF2, however, and in these patients, non-vestibular presentations predominate, including visual symptoms (cataracts, retinal hamartoma, or optic nerve sheath meningioma), cutaneous lesions (NF2 skin plaques, cutaneous schwannomas, or hyperpigmented lesions), transient mononeuropathy of cranial nerves, seizures (often with focal cortical dysplasia), and symptomatic spinal nerve root

Figure 1 Radiographic features of the case



(A) Aggressive growth pattern of tumors. Note the enhancement in the left middle cerebellar peduncle on August 12, 2016, in the region of T2-weighted signal change. (B) T2 fluid attenuation inversion recovery changes across time. The earlier lesion in 2015 has enlarged and shows enhancement. Biopsy in this region showed necrosis but was negative for tumor or infection. (C) Time course of spreading ADC changes. The duration of depressed ADC is atypically long compared with the phasic pattern usually seen in acute stroke. ADC = apparent diffusion coefficient.

schwannomas.[1,2] We recently encountered a patient with progressive brainstem necrosis, as shown on serial diffusion-weighted images and by biopsy. Seven prior published cases had marked similarities, suggesting an underrecognized syndrome in NF2.

Methods

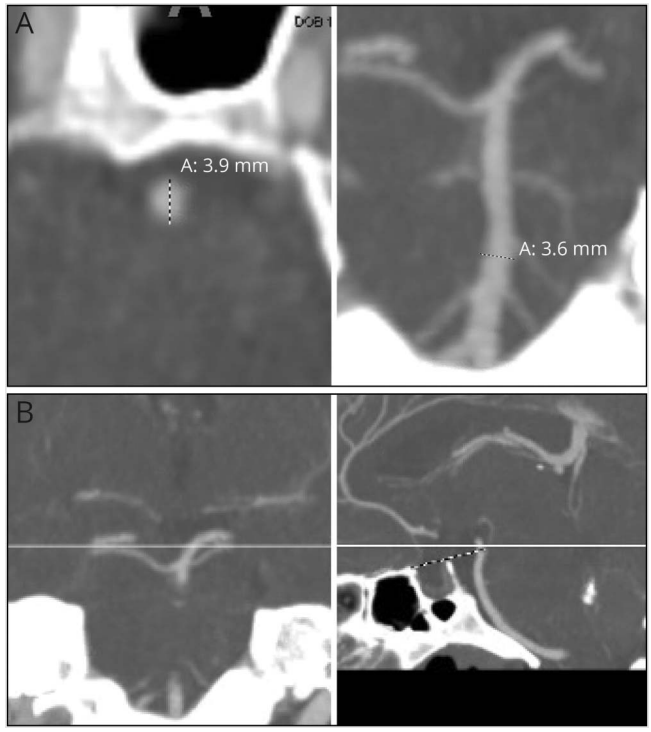
We performed a detailed case review including clinical and neuroimaging analyses, genetic testing, and brain biopsy. Multicase analysis was undertaken to observe common features in 16 predetermined categories.[3–6]

Results

Clinical data

A 25-year-old woman with a history of strabismus surgery in childhood developed episodes of vertigo. After 6 months of persistent symptoms, imaging revealed bilateral vestibular and other cranial nerve schwannomas, multiple meningiomas and a cervical cord ependymoma, as well as several small focal white matter lesions in the corona radiata. There was a subtle, nonenhancing focus of T2-weighted hyperintensity in the L middle cerebellar peduncle on a December 2015 MRI, adjacent to a subsequent area of restricted diffusion (figure 1). There was no family history of NF2, although the parents were not tested or imaged. Single gene testing of blood lymphocytes detected a germline *NF2* variant, c.288_290delCTT, which deletes a highly conserved proline residue and is thought to inactivate merlin. A large left lumbar schwannoma raised concern for malignant peripheral nerve sheath tumor and was partially resected via an abdominal approach. There was substantial blood loss requiring transfusion and volume support. Ten days later, she developed progressive slurred speech, left facial numbness, bilateral hand weakness, and difficulty walking. Blood pressure and serum sodium were normal. She progressed to a locked-in syndrome over 4 days with some residual eye movements. Serial MRIs revealed a multifocal, bilateral, spreading area of markedly hypointense apparent diffusion coefficient (ADC) signal (0.3×10^{-3} mm^2/s) in the pons and left middle cerebellar peduncle (figure 1). At the site of the prior T2 signal change in the left middle cerebral peduncle, there was subtle enhancement where ADC was less decreased. Vascular imaging, including CT angiogram and a catheter angiogram, showed a basilar artery diameter of 3.9 mm at the mid pons and a basilar bifurcation at the level of the dorsum sellae (figure 2, A and B) and was midline throughout, thus not meeting a definition of dolichoectasia.[7–9] The anatomy of the basilar artery did not change as seen 5 years later on the 2020 MRI study. Serial ADC maps showed prolonged loss of signal over time rather than the typical phasic pattern seen after ischemic stroke. Perfusion maps suggested decreased cerebral blood volume and cerebral blood flow in the lesion (data not presented). CSF showed a WBC of 5 cells per mm^3 but was otherwise normal including nucleic acid amplification tests for viral infection. Biopsy of the left middle cerebellar peduncle in the area of initial enhancement revealed white matter, which varied from near-normal to necrotic. Within the latter, there was evidence of axonal swelling, mild macrophage infiltration, and scant lymphocytes. Luxol fast blue–Periodic acid–Schiff stain showed focal loss of myelin staining but with some fragments showing normal myelin. No vascular pathology was identified. PCR analysis of tissue for infection was negative. Fluorodeoxyglucose-PET 1 month after the onset showed hypometabolism in the pons. Subsequent MRIs demonstrated some persistent restricted diffusion as well as encephalomalacia of the basis pontis and rapid growth of multiple NF2-related tumors. Four years later, the patient is locked-in except for upgaze and is deaf in both ears. A mammalian target of rapamycin inhibitor was started in an attempt to suppress further growth of the tumors.[10,11]

Figure 2 Vascular imaging



(A) Diameter of the basilar artery at mid pons. The maximal diameter of 3.9 mm did not meet the 4.5-mm threshold for dolichoectasia. The course of the basilar artery was midline. (B) Tip of the basilar artery. The basilar artery bifurcated at the level of the dorsum sellae and thus did not meet the criteria for elongation. Note the persistent right fetal posterior cerebral artery.

Syndrome features

Table 1 shows the findings of 8 cases with regard to 16 predetermined categories of clinical, imaging, genetic, and pathologic features.[3–6] In addition, a 2019 article from a UK group described 2 pediatric patients, without clinical details, who had pontine infarcts. One had renal artery stenosis and coarctation of the aorta, and a second had vertebral artery stenosis and a 22q microdeletion.[12] Table 2 shows an analysis of the *NF2* variants reported in each case. Overall, the similarities between cases are striking.

Table 1 Features of the syndrome

Major features	Cases (n = 8)	Syndrome average (95% CI)
Sex		60% female
Male	2	
Female	3[a]	
Unknown	3	
Age at dx NF2, y	2, 4, 6, 7, 13, 13, 22, 25[a]	11.5 (4.5–18.5)
Age at brainstem event, y	2, 4, 7, 13, 13, 15, 22, 25[a]	12.6 (5.5–19.5)
Genetic alteration	c.114G>A (splice donor, VUS); c.115-1G>C (null); c.169C>T (null); NF1 neg; c.288_290delCTT[a]; c.447+1G>A (null); c.448-1G>A (null); frameshift, exon 12; deletion exon2	Typical null variants in NF2
De novo	Y, Y[b], Y[b], Y[b], Y[b], Y[b], Y[a]; N	Usually de novo
Severity of NF2	M; S, S, S, S, S, S, S[a]	Severe
Unusual lesions for NF2	N, N, N, N, N, N; Cb Ca++, No VS, E, cauda; white matter lesions[a]	Occasional
Brainstem compression by VS at event	N, N, N, N, N, N, N, N[a]	No
Precipitating event	Diarrhea; fever, cough; menorrhagia; blood loss after pelvic surgery[a]; no; NR, NR, NR	Yes, possibly hypoperfusion
Onset	AM, AM, AM, AM, AM, AM; AP[a]; asymptomatic	Acute, monophasic
Localization in brainstem		Left-sided predominant pons, midbrain
Midbrain	MB, MB, MB	
Pons	P, P, P, P, P, P[a]	
Medulla	MD	
Unilateral	U, U, U	
Bilateral	B[a]	
Left	L, L, L, L, L[a]	
Right	R, R, R[a]	
Clinical severity	M, M, M, M; S, S, S, S[a]	Mild to severe
HTN at onset	N, N, N, N, N, N, N[a]; NR, NR	No
Vascular imaging	Neg, Neg, Neg, Neg, Neg, Neg[a]; narrowing left ICA; small left MCA	Normal; rarely narrowed lumen ICA or MCA
Stroke blood testing	Neg, Neg, Neg, Neg, Neg, Neg[a]; NR, NR	Negative
Biopsy features	Reactive astrogliosis, microglia, hyalinized large caliber vessels; necrosis, vessels normal[a]	Necrosis; vessels normal

Abbreviations: AM = acute monophasic; AP = acute progressive; B = bilateral; Cb-Ca++ = cerebellar calcification; CI = confidence interval; E = ependymoma; HTN = hypertension; ICA = internal carotid artery; M = mild; MB = midbrain; MCA = middle cerebral artery; MD = medulla; N = no; Neg = negative; NR = not reported; P = pons; S = severe; U = unilateral; VS = vestibular schwannoma.
[a] Present case.
[b] Likely but not explicitly stated.

To summarize the data, the syndrome of brainstem necrosis in juvenile NF2 typically occurs in teenagers without previously known NF2 as an acute, typically monophasic event in the midbrain or pons. Some patients have had a recent hypoperfusion event. MRI shows markedly restricted diffusion in the lesion, but vascular imaging is normal. Our case demonstrated evolution of imaging findings and showed some unusual features compared with acute stroke. NF2 imaging features are apparent at the time of diagnosis. Typical null *NF2* alterations are seen, and absence of family history in most cases suggests a de novo mutation. Biopsy in 2 cases, including ours, shows necrosis without small vessel pathology. The early-onset, high number of NF2-related lesions at diagnosis and the subsequent rapid growth suggest an

Table 2 Analysis of alterations

Alteration	Effect	ACMG variant classification[16,17]	gnomAD allele frequency	MutationTaster binary prediction[18]
c.114G>A NM_000268.4[a]	Alteration within used splice site	Pathogenic: PVS1, PM1, PM2, BP4	0%	Disease causing
c.115-1G>C NM_000268.4[a]	Alteration within used splice site	Pathogenic: PVS1, PM2, PP3	0%	Disease causing
c.169C>T NM_000268.4[a]	Nonsense	Pathogenic: PVS1, PM1, PM2, PP3, PP5	0%	Disease causing
c.288_290delCTT[b] NM_000268.4	Substitution of highly conserved proline	Likely pathogenic: PM1, PM2, PM4, PP3, PP5	0%	Disease causing
c.447+1G>A NM_000268.4[a]	Alteration within used splice site	Pathogenic: PVS1, PM2, PP3	0%	Disease causing
c.448-1G>A NM_000268.4[a]	Alteration within used splice site	Pathogenic: PVS1, PM2, PP3	0%	Disease causing
Frameshift, exon 12	Truncating	NA	NA	NA
Deletion exon 2	Truncating	NA	NA	NA

Abbreviations: ACMG = American College of Medical Genetics; gnomAD = Genome Aggregation Database; NA = not available.
[a] Probable transcript but not explicitly stated in reference.
[b] Current case.

aggressive form of NF2 in these patients as is often seen in younger patients.

Discussion

There are remarkable similarities between the cases in the literature and our patient, and this suggests a discrete clinical syndrome of which pediatric neurologists and stroke neurologists should be aware. The name brainstem ischemic syndrome in juvenile NF2 is proposed for this rare syndrome.

Our patient seems to have the most clinically devastating course of those reported to date, and despite the similarities in the cases, there are some distinctive features, which may be of value. Our patient was of somewhat older age. Gradual progression over 4 days to a severe neurologic syndrome with spreading restricted diffusion, rather than the monophasic courses reported before, is also unusual. Perfusion imaging in our patient showed low cerebral blood flow and blood volume in the pons, but it was difficult to be certain that ischemia was the cause of the perfusion changes, and the bilateral progression, the atypically long phasic course of the restricted diffusion, and the absence of vascular findings on imaging and biopsy argue against ischemia as the cause. The known focus of abnormal T2-weighted hyperintensity in the left middle cerebellar peduncle that was adjacent to the restricted diffusion had enlarged at the time of presentation and showed enhancement, and this seemed likely to represent a tumor, but biopsy of the area did not support this. Acute vacuolization of myelin, including that seen with central pontine myelinolysis (CPM), can produce restricted diffusion but not usually to the degree found in these cases. The asymmetric distribution of lesions in the pons was also not consistent with CPM, and there was no electrolyte abnormality. Delayed hypoxic leukoencephalopathy can show a long course of markedly restricted diffusion, but has not been described in the brainstem, and the preceding events in the patients here were not consistent with this mechanism. An infectious process seems unlikely given the benign CSF profile and negative PCR testing. Finally, our patient had deletion of a highly conserved proline rather than the truncating mutation more commonly seen in the other cases and in patients with NF2 in general. Nonetheless, this deletion likely produced a loss of function in merlin in common with null mutants.

There have been rare cases in which angiographic narrowing of the internal carotid artery,[6] middle cerebral artery (with middle cerebral artery infarct),[13] vertebral artery,[12] aorta,[12] or renal artery[14] has been seen in NF2, leading those authors to propose a vascular process. Although well known in NF1, vasculopathy is not clearly recognized in young patients with NF2 at this time.[1,2,12] Progressive brainstem stroke syndromes have been seen with dolichoectasia of the basilar artery in NF1.[15] Our patient did not meet the criteria for dolichoectasia. It is notable that these brainstem ischemic events occur in such close anatomic proximity to the uniquely selective development of vestibular schwannomas in NF2. Given the rarity of the syndrome of brainstem ischemic syndrome in juvenile NF2, it is possible that a digenic process is at work. One of the literature reports analyzed the *NF1* gene and found no alterations. Whole-exome sequencing would be a reasonable consideration in these cases.

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Disclosure

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Appendix Authors

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Tara Benkers, MD	Ivy Center for Advanced Brain Tumor Treatment; Swedish Neuroscience Institute	Clinical management of the patient and input on the manuscript
Connor McCormick, MD	University of Washington School of Medicine	Identification of literature cases and input on the manuscript

References

1. Anand G, Vasallo G, Spanou M, et al. Diagnosis of sporadic neurofibromatosis type 2 in the paediatric population. Arch Dis Child 2018;103:463–469.
2. Gaudioso C, Listernick R, Fisher MJ, Campen CJ, Paz A, Gutmann DH. Neurofibromatosis 2 in children presenting during the first decade of life. Neurology 2019;93:e964–e967.
3. Ng J, Mordekar SR, Connolly DJA, Baxter P. Stroke in a child with neurofibromatosis type 2. Eur J Paediatr Neurol 2009;13:77–79.
4. Sreedher G, Panigrahy A, Ramos-Martinez SY, Abdel-Hamid HZ, Zuccoli G. Brachium pontis stroke revealing neurofibromatosis type-2. J Neuroimaging 2013;23:132–134.
5. Gugel I, Mautner VF, Kluwe L, Tatagiba MS, Schumann MU. Cerebrovascular insult as presenting symptom of neurofibromatosis type 2 in children, adolescents, and young adults. Front Neurol 2018;9:733.
6. Lascelles K, Afridi S, Siddiqui A, Hemingway C, Ferner R, Ganesan V. Cerebral vasculopathy in childhood neurofibromatosis type 2: cause for concern? Dev Med Child Neurol 2018;60:1285–1288.
7. Smoker WR, Price MJ, Keyes WD, Corbett JJ, Gentry LR. High-resolution computed tomography of the basilar artery: 1. Normal size and position. Am J Neuroradiol 1986;7:55–60.
8. Smoker WR, Corbett JJ, Gentry LR, Keyes WD, Price MJ, McKusker S. High-resolution computed tomography of the basilar artery: 2. Vertebrobasilar dolichoectasia: clinical-pathologic correlation and review. Am J Neuroradiol 1086;7:61–72.
9. Forster A, Ssozi J, Al-Zghloul M, Brockmann MA, Keri HU, Groden C. A comparison of CT/CT angiography and MRI/MR angiography for imaging of vertebrobasilar dolichoectasia. Clin Neuroradiol 2014;24:347–353.
10. Goutagny S, Raymond E, Esposito-Farese M, et al. Phase II study of mTORC1 inhibition by everolimus in neurofibromatosis type 2 patients with growing vestibular schwannomas. J Neurooncol 2015;122:313–320.
11. Karajannis MA, Legault G, Hagiwara M, et al. Phase II study of everolimus in children and adults with neurofibromatosis type 2 and progressive vestibular schwannomas. Neuro Oncol 2014;16:292–297.
12. Halliday D, Emmanouil B, Vassallo G, et al. Trends in the phenotype in the English paediatric neurofibromatosis type 2 cohort stratified by genetic severity. Clin Genet 2019;96:151–162.
13. Ryan A, Hurley M, Brennan P, Moroney JT. Vascular dysplasia in neurofibromatosis type 2. Neurology 2005;65:163–164.
14. Cordeiro NJV, Gardner KR, Huson SM, et al. Renal vascular disease in neurofibromatosis type 2: association or coincidence? Dev Med Child Neurol 2006;48:58–59.
15. Giannantoni NM, Broccolini A, Frisullo G, et al. Neurofibromatosis type 1 associated with vertebrobasilar dolichoectasia and pontine ischemic stroke. J Neuroimaging 2015;25:505–506.
16. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–424.
17. Kopans C, Tsiolkas V, Kouris A, et al. VarSome: the human genomic variant search engine. Bioinformatics 2018;25:1978–1980.
18. Schwarz JM, Cooper DN, Schuelke M, et al. MutationTaster2: mutation prediction for the deep-sequencing age. Nat Methods 2014;11:361–262.