A Rare Report of the Coexistence of Sickle Cell Disease, Neurofibromatosis Type 1, and Intracranial Hypertension in a Pediatric Patient.

Amie Patel[1], Timothy Winter[1], and Akshat Jain[1]

[1]Loma Linda University Medical Center

March 07, 2024

Abstract

A 8 year-old female with sickle cell disease diagnosed at birth was confirmed to have neurofibromatosis type 1 at 13 months of age. At 7 years old, she was noted to have incidental papilledema with subsequent workup showing elevated opening pressure. She was diagnosed with intracranial hypertension and began treatment with acetazolamide and the discontinuation of hydroxyurea. Acetazolamide was tapered off and hydroxyurea was restarted with no worsening in her ophthalmologic exam. We report this case due to the rare occurrence of all three conditions as well as delineate the complications that can occur with the combination of diseases.

A Rare Report of the Coexistence of Sickle Cell Disease, Neurofibromatosis Type 1, and Intracranial Hypertension in a Pediatric Patient.

Amie Patel[1], Timothy Winter[2], Akshat Jain[1, 3]

[1] Division of Pediatric Hematology Oncology, Department of Pediatrics, Loma Linda University School of Medicine, corresponding author: akjain@llu.edu

[2] Loma Linda University Eye Institute

[3] Loma Linda University School of Public Health

Correspondence to:

Akshat Jain, MD

2195 Club Center Dr., Suite E, San Bernardino, CA 92408

akjain@llu.edu

Telephone: +1-909-5558-0099

Abstract Words: 99

Manuscript Words: 1046

Figures : 1

Tables : 1

Supporting Information:

Figures : 2

Short Running Title : Coexistence of Three Conditions

Keywords : sickle cell, intracranial hypertension, neurofibromatosis

Abbreviations :

SCD	Sickle Cell Disease
NF1	Neurofibromatosis Type 1
IH	Intracranial Hypertension
RNFL	Retinal Nerve Fiber Layer
PHOMS	Peripapillary Hyperreflective Ovoid Mass-like Structures
OCT	Optical Coherence Tomography

Abstract

A 8 year-old female with sickle cell disease diagnosed at birth was confirmed to have neurofibromatosis type 1 at 13 months of age. At 7 years old, she was noted to have incidental papilledema with subsequent workup showing elevated opening pressure. She was diagnosed with intracranial hypertension and began treatment with acetazolamide and the discontinuation of hydroxyurea. Acetazolamide was tapered off and hydroxyurea was restarted with no worsening in her ophthalmologic exam. We report this case due to the rare occurrence of all three conditions as well as delineate the complications that can occur with the combination of diseases.

Introduction

Neurofibromatosis type 1 (NF1), also called von Recklinghausen's disease, is a common neurocutaneous disorder that is caused by inheritance or a de novo mutation. The mutation occurs in the protein, neurofibromin, which functions similarly to a tumor suppressor gene. Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy caused by a single gene mutation in beta globin. SCD is one of the most common red blood cell disorders with an approximate incidence of one out of 365 African Americans born each year.

The co-existence of SCD and NF1 is rare with only two reported cases[1-2]. One report was in a 15 year old patient who developed an optic glioma, renal artery stenosis, large facial plexiform neurofibromas, and bilateral lower extremity osteomyelitis[1]. The other report was in a 28 year old who had multiple cutaneous neurofibromas, lisch nodules, splenomegaly, hyperbilirubinemia, and pulmonary tuberculosis[2].

Individuals with NF1 have been reported to have intracranial hypertension (IH) caused only by mass or stenosis[3]. Cases of IH have been reported in individuals with sickle cell disease thought to be mostly caused by increased fetal hemoglobin concentration from hydroxyurea[4-5]. The current report of a patient presenting with SCD, NF1 and IH has never been reported.

Case Report

An 8 year-old African American female with severe sickle cell (HgSS) disease diagnosed at birth was confirmed to have NF1 at 13 months of age with > 6 cafe au lait macules over 5mm in diameter, freckling in the axillary regions (Crowe's sign) and significant family history as the mother of child has 6 other children, 3 of whom have NF1 including herself. The patient's SCD course was complicated by splenic sequestration necessitating splenectomy at 3 years of age. She was started on Hydroxyurea at 5 years of age and since has had a good hematologic and clinical response in that she did not require hospitalizations or emergency intervention for a severe vaso-occlusive crisis. She followed with ophthalmology annually to screen for ophthalmologic associations with SCD and NF1 beginning at age 6 years. She was also seen by neurology to evaluate for possible brain vasculopathies as well as learning delays associated with NF1. Routine brain imaging surveillance with MRI/MRA had been normal except for a T2 hyperintensity in the right frontal lobe periventricular white matter related to a remote infarct and slightly prominent lenticulostriate vessels noted initially when she was 5 years of age (Supplemental Fig. S1). She has been neurologically asymptomatic.

When she was 7 years of age, she was noted to have incidental papilledema. Subsequent work up revealed MRI/MRA brain w/wo contrast and MRI orbits w/wo showed no masses or new changes compared to prior imaging. A lumbar puncture was then performed showing an opening pressure of 34cm H2O confirming the clinical suspicion of IH. She was asymptomatic at the time, but was started on 250 mg PO BID of acetazolamide orally while at the same time the hydroxyurea was discontinued, as reports had shown high fetal hemoglobin could cause intracranial hypertension. Her fetal hemoglobin was 30.5% which was otherwise an ideal response to the disease modifying agent in a patient with severe SCD.

Papilledema was noted to persist several weeks after starting acetazolamide, so the dose was titrated up and the patient was referred for pediatric neuro-ophthalmic evaluation. Ancillary testing performed 3 months later during pediatric neuro-ophthalmic evaluation confirmed normal retinal nerve fiber layer (RNFL) analysis with mild peripapillary hyperreflective ovoid mass-like structures (PHOMS) at the present dose of acetazolamide 425 mg PO BID (Fig. 1). The patient was then tapered off acetazolamide over the period of 1 month, and repeat testing performed 7 months later confirmed presence of normal RNFL analysis in both eyes with congenital anomaly of both optic nerves (Supplemental Fig. S2). Since optical coherence tomography (OCT) RNFL was normal and the patient continued to have no symptoms, hydroxyurea was restarted 5 months after initial diagnosis of IH and her fetal hemoglobin at that time was 15.7%. Table 1 shows her hemoglobin electrophoresis trend. She has been feeling well with no worsening in the ophthalmological exam while off acetazolamide.

Discussion

Both NF1 and SCD individually may cause unique complications that when combined can be worsened. Patients with sickle cell disease have an increased risk of vasculopathies. NF1 has been shown to increase the risk of peripheral and cerebral vascular abnormalities in the pediatric patient. Neurofibromatosis type 1-associated vasculopathy is an acquired condition that can affect all sized vasculature, most notably causing aneurysms or stenoses of the aortic, renal and mesenteric circulation[6]. Therefore, routine screening for hypertension is recommended due to renovascular disease as well as coarctation of the aorta[7]. Additionally, moyamoya disease and other cerebral vasculopathies have been routinely observed; therefore, screening with an MRV/MRA brain is recommended for evaluation of moyamoya, arteriovenous malformation, and strokes[8].

Similarly, SCD increases the risk of micro and macro vasculopathies, which causes the development of pulmonary hypertension, stroke, leg ulcerations, priapism, and other organ dysfunctions[9]. In this patient, her MRI brain showed a remote infarct in the right frontal lobe showing a silent stroke. Both her NF1 and SCD increases her risk of having strokes, pulmonary hypertension, and other vascular complications that need routine screening[9-11].

IH can be caused by cerebral vascular abnormalities including intracranial venous sinus thrombosis and venous sinus stenosis[12]. Several reports have shown occurrence of cerebral venous and sinus thrombosis in SCD and NF1[13-14]. Other causes of intracranial hypertension in NF1 include intracranial mass as well as aqueductal stenosis[3,15]. This patient had no vascular or structural abnormality noted on brain imaging.

Many studies have shown a relationship between IH and SCD[4-5]. Hydroxyurea increases fetal hemoglobin, which has been reported to cause IH and increased risk of cerebral vascular abnormalities[16-17]. When hydroxyurea was discontinued, the IH improved in some patients[4-5]. In our patient, after discontinuing hydroxyurea and starting acetazolamide, her OCT RFNL became normal. Her fetal hemoglobin dropped to 15.7%. We are unable to determine if hydroxyurea was the cause of IH or if she developed idiopathic intracranial hypertension, since the increased pressure resolved with both the discontinuation of hydroxyurea and usage of acetazolamide. Prospective evaluation of patients such as the one presented are needed in order to determine if increases in fetal hemoglobin cause IH or if another etiology may be to blame. Additionally, more genetic studies are needed to show if there is a link between NF1 and SCD.

Conflict of Interest

All authors report no disclosures.

References

1. Alanazi, Alanazi N AI, Almoosa Z, Iqbal Z. First report of coexistence of sickle cell disease and neurofibromatosis Type 1 in a Saudi patient with family history of neurofibromatosis Type 1. 2019.
2. Vanka P, Tejavath R, Chandra N, Swaroopa D, Subbalaxmi M, Yedla D. A rare case report of coexistent neurofibromatosis type 1 with sickle cell beta-plus thalassaemia. Journal of Clinical and Scientific Research. 2020;9(45).
3. CrÈange A, Zeller J, Rostaing-Rigattieri S, et al. Neurological complications of neurofibromatosis type 1 in adulthood. Brain. 2021;122(3):473-481.
4. Segal L, Discepola M. Idiopathic intracranial hypertension and sickle cell disease: two case reports. Can J Ophthalmol. 2005 Dec;40(6):764-7. doi: 10.1016/S0008-4182(05)80097-3. PMID: 16391644.
5. Henry M, Driscoll MC, Miller M, Chang T, Minniti CP. Pseudotumor Cerebri in Children With Sickle Cell Disease: A Case Series. 2004;113(3):e265-e269.
6. Oderich GS, Sullivan TM, Bower TC, Gloviczki P, Miller DV, Babovic-Vuksanovic D, Macedo TA, Stanson A. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. J Vasc Surg. 2007 Sep;46(3):475-484. doi: 10.1016/j.jvs.2007.03.055. Epub 2007 Jul 30. PMID: 17681709.
7. Booth C, Preston R, Clark G, Reidy J. Management of renal vascular disease in neurofibromatosis type 1 and the role of percutaneous transluminal angioplasty. *Nephrology Dialysis Transplantation.* 2002;17(7):1235-1240.
8. Serafini NB SC, Vinhas AS, Godinho MB. Moyamoya syndrome associated with neurofibromatosis type 1 in a pediatric patient. 2017;92(6):870-873.
9. Usmani A, Machado RF. Vascular complications of sickle cell disease. *Clin Hemorheol Microcirc* . 2018;68(2-3):205-221. doi:10.3233/CH-189008
10. Jutant E-M, Girerd B, JaÔs X, et al. Pulmonary hypertension associated with neurofibromatosis type 1. 2018;27.
11. Benneh-Akwasi Kuma A O-AAM, Sey F, Olayemi E, Nouraie M, et al. Prevalence of relative systemic hypertension in adults with sickle cell disease in Ghana. 2018;13(1).
12. Mercille G, Ospina LH. Pediatric Idiopathic Intracranial Hypertension. 2007;28(11):e77-e86.
13. Rahimi Z, Parsian A. Sickle cell disease and venous thromboembolism. Mediterr J Hematol Infect Dis. 2011;3(1):e2011024. doi: 10.4084/MJHID.2011.024. Epub 2011 May 24. PMID: 21713075; PMCID: PMC3113276.
14. Terry AR, Jordan JT, Schwamm L, Plotkin SR. Increased Risk of Cerebrovascular Disease Among Patients With Neurofibromatosis Type 1: Population-Based Approach. Stroke. 2016 Jan;47(1):60-5. doi: 10.1161/STROKEAHA.115.011406. Epub 2015 Dec 8. PMID: 26645253.
15. Pascual-Castroviejo I, Pascual-Pascual SI, Velázquez-Fragua R, Viaño J, Carceller-Benito F. Estenosis del acueducto de Silvio en la neurofibromatosis tipo 1. Presentación de 19 pacientes infantiles [Aqueductal stenosis in the neurofibromatosis type 1. Presentation of 19 infantile patients]. Rev Neurol. 2007 Jul 1-15;45(1):18-21. Spanish. PMID: 17620261.
16. Rigano P, Pecoraro A, Calvaruso G, Steinberg MH, Iannello S, Maggio A. Cerebrovascular events in sickle cell-beta thalassemia treated with hydroxyurea: a single center prospective survey in adult Italians. Am J Hematol. 2013 Nov;88(11):E261-4. doi: 10.1002/ajh.23531. Epub 2013 Aug 30. PMID: 23828131.
17. Chamouine A ST, Muszlak M, et al. High fetal hemoglobin level is associated with increased risk of cerebral vasculopathy in children with sickle cell disease in Mayotte. BMC Pediatr. 2020;20(1):302.

Legends

FIGURE 1 OCT RNFL of both eyes suggesting normal findings (A & B) with enhanced depth imaging (C) showing PHOMS temporally in the right eye consistent with resolving optic disc edema.

SUPPLEMENTAL FIGURE S1 Regular T2 MRA brain showing a T2 hyperintensity in the right frontal lobe periventricular white matter related to a remote infarct.

SUPPLEMENTAL FIGURE S2 Repeat OCT RNFL (top) off all acetazolamide and fundus photography (bottom) show congenital anomaly of both optic nerves.

Hosted file

`Table 1.docx` available at https://authorea.com/users/730391/articles/710121-a-rare-report-of-the-coexistence-of-sickle-cell-disease-neurofibromatosis-type-1-and-intracranial-hypertension-in-a-pediatric-patient