Weakness, Anemia, and Neutropenia in a 9-Year-Old Girl With Influenza

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A previously healthy 9-year-old immigrant girl from Mexico was evaluated in the emergency department (ED) with one week of fatigue, fevers, rhinorrhea, and cough. She initially presented to her primary pediatrician, where a complete blood count revealed neutropenia, prompting referral to the ED. In the ED, she was found to be influenza A–positive. Because of dehydration, she received intravenous fluids and was admitted to the pediatric hospital medicine service. After 2 days, influenza symptoms improved, and oral intake increased. However, she was noted to have decreased bilateral lower-extremity strength, absent Achilles reflexes, decreased lower-extremity sensation and proprioception, a positive result on the Romberg sign, and abnormal heel-to-shin testing results. These findings prompted an urgent neurology consultation. After extensive imaging, laboratory evaluation, and further consultations, a diagnosis was established.

CASE HISTORY WITH SUBSPECIALTY INPUT

Dr Cohen, Pediatric Hospital Medicine Fellow, Moderator

A previously healthy 9-year-old girl presented to the emergency department (ED) with 12 days of symptoms that included fatigue, congestion, cough, and fever. She presented to her primary pediatrician 9 days before and was started on amoxicillin for acute otitis media. Despite adherence to the antibiotics, she developed progressive lower-extremity weakness and pain, worsening fatigue, and emesis. On the day of presentation, she developed a fever to 39.5°C. She also refused to walk because of weakness. She was reevaluated by her pediatrician and was found to be neutropenic, prompting referral to the ED. On further history, the patient had been exposed to an aunt with an influenza-like illness just before onset of symptoms.

In the ED, she was found to be influenza A–positive and had an absolute neutrophil count (ANC) of 900 cells per μL, with a normal hemoglobin level and a normal platelet count. She was initially febrile to 39.5°C, with a pulse of 134 beats per minute and blood pressure of 136/61 mm Hg. After a 20-mL/kg normal saline bolus and antipyretic administration, her energy and vital signs improved. However, she still felt weak when walking. She was started on oseltamivir and admitted to the pediatric hospital medicine service for further supportive care.

Dr Owolabi, what is your typical admission criteria for influenza, and how do you manage a child with influenza admitted to the hospital? Does this patient's neutropenia change your approach to their condition?

Dr Funmilola Owolabi, Pediatric Hospital Medicine

Hospitalization may be necessary if a child develops severe symptoms or complications of influenza. Nausea and

abstract

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Dr Cohen initiated this collaborative project, reviewed the literature, recruited and interviewed all subspecialists, and drafted and edited the manuscript; Dr Foradori initiated this collaborative, supervised the recruitment of subspecialists, and critically revised the manuscript; Drs Dowdell-Smith, Laufman, and Iacobas contributed to the writing and revision of the manuscript; Drs Bass and Owolabi initiated this collaborative, supervised the recruitment of the subspecialists, and contributed to the writing and revision of the manuscript; and all authors were involved in the patient's care, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2019-2574

Accepted for publication Nov 7, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Cohen A, Owolabi FS, Dowdell-Smith CP, et al. Weakness, Anemia, and Neutropenia in a 9-Year-Old Girl With Influenza. *Pediatrics*. 2019; 145(5):e20192574

vomiting, 2 commonly presenting symptoms in children, can lead to dehydration, prompting the need for intravenous hydration. Upper respiratory symptoms can progress to lower airway disease, leading to hypoxemia and respiratory distress necessitating supplemental oxygen or a higher level of respiratory support. Concern for a bacterial superinfection may prompt initiation of antibiotics. Children with underlying chronic illnesses, such as asthma, congenital heart disease, or immunosuppression, are at higher risk of complications and therefore can require closer monitoring.[1] Ultimately, the need for additional supportive care outside of oral rehydration, antipyretics, and bed rest is indicative of a more severe illness and likely a need for hospitalization.

Although management is primarily supportive, national guidelines recommend that children hospitalized with influenza should be treated with oseltamivir regardless of their duration of symptoms.[2] In reality, antiviral use in children hospitalized with influenza varies by practice.[3] Concerns regarding the side-effect profile of antiviral agents, the subjective classification of "severe disease," and overall perceived benefits may impact provider prescribing behaviors.[4] Our patient was started on oseltamivir at the time of admission and completed a 5-day course during her hospitalization.

The patient's neutropenia did not change my initial approach. At the time of admission, neutropenia was moderate (ANC of 900 cells per μL). In the setting of a viral infection, neutropenia can be caused by transient bone marrow suppression[5,6] and therefore should resolve. Persistent neutropenia after illness resolution or the development of concomitant anemia or thrombocytopenia, however, would broaden my differential.

Dr Cohen

The patient arrived at the inpatient unit of the hospital and was noted to be well-appearing. Vital signs included a temperature of 37.7°C, a pulse of 108 beats per minute, and a blood pressure of 104/59 mm Hg. The patient's weight was at the fifth percentile for age, her height was at the 43rd percentile for age, and her BMI was at the first percentile for age. She was thin but well hydrated, with normal cardiac, pulmonary, and abdominal examination results. At that point, gait was not assessed.

Over the next 3 days, her influenza symptoms of fever and emesis both improved. She was noted to have adequate lower-extremity muscle strength. Myalgias of the lower extremities improved, but she was requiring some assistance to walk. Intravenous fluids were weaned, and pain was controlled on oral medications. Before discharge, her ambulation was more formally evaluated and revealed a broad-based gait with poor balance and inability to ambulate independently. Bilateral lower-extremity strength was 4/5, with absent Achilles reflexes bilaterally but 2+ patellar reflexes. She also had grossly decreased lower-extremity sensation and proprioception, a positive result on the Romberg sign, and abnormal heel-to-shin testing results. Lower-extremity musculature was mildly tender.

Dr Owolabi, what was your thought process when confronted with these new examination findings?

Dr Owolabi

The patient's inability to walk, weakness, and muscle tenderness were initially thought to be secondary to viral myositis. In the setting of influenza, myositis is commonly reported in the calves and may impact weight bearing.[2] However, her creatinine kinase level was normal, and ambulation remained severely limited despite improvement in her other symptoms of influenza. Additional examination findings were concerning for an underlying neurologic process, yet the primary cause of dysfunction was difficult to pinpoint. There were concerns for cerebellar, proprioceptive, and even possible lower motor neuron or peripheral sensory dysfunction on the basis of her examination. Given the reason for her initial hospitalization, postinfectious etiologies, such as acute cerebellar ataxia and Guillain-Barré syndrome, were highest on the differential.

At this point, pediatric neurology was consulted.

Dr Cohen

Dr Dowdell-Smith, how do you distinguish between the different etiologies of abnormal gait? Is this an area in which your examination can help you "localize" the lesion?

Dr Cicely Dowdell-Smith, Pediatric Neurology

Abnormal gait is a general description. Therefore, using specific terminology is important when requesting consultation. The differential diagnosis varies widely for a child with an abnormal gait depending on whether it is due to a limp, ataxia, or weakness. Weakness may cause a staggering and off-balance gait that is not truly ataxic. In this case, the hospitalist was clearly describing an ataxic gait, which is often described as wide based and drunken. The differential diagnosis for this type of gait is broad and also includes sensory ataxia from proprioceptive impairments.

On the basis of the patient's recent influenza infection, the first thought in this patient was acute cerebellar ataxia. This diagnosis accounts for up to 50% of all cases of cerebellar ataxia.[7] However, acute cerebellar ataxia is a diagnosis of exclusion. An additional postinfectious etiology of ataxia is Guillain-Barré syndrome, an

immune-mediated polyneuropathy most commonly presenting as ascending weakness. Intracranial etiologies of acute ataxia include brainstem and cerebellar tumors, intracranial infection, ischemic or hemorrhagic stroke, and intracranial demyelinating processes. Additionally, toxin exposure, inborn errors of metabolism (IEMs), and trauma also can cause acute onset of ataxia but were felt to be less likely on the basis of this patient's presentation.

Additional findings on the physical examination may be helpful in trying to localize the origin of neurologic signs and symptoms. It is always important to recognize abnormal vital signs as a potential indicator of increased intracranial pressure. Abnormal mental status may suggest acute disseminated encephalomyelitis or intracranial infection. Headaches, vomiting, focal neurologic abnormalities, cranial neuropathies, or papilledema are associated with posterior fossa tumors. Findings specific to the cerebellum include speech abnormalities, difficulty with coordination of voluntary movement (finger to nose, dysdiadochokinesia), and tremor. Fevers are typically associated with infectious causes such as meningitis, encephalitis, labyrinthitis, and intracranial abscesses. Guillain-Barré syndrome typically presents with symmetric ascending weakness, decreased or absent reflexes, and sensory symptoms. The Miller-Fisher variant may present differently with external ophthalmoplegia, ataxia, and areflexia.

Dr Cohen

We obtained an MRI of the brain and spine with and without contrast. The MRI of the brain was normal. However, the MRI of the spinal cord revealed symmetric, bilateral T2 signal intensity within the dorsal columns from the level of C2 to at least the level of T2, although artifact made it difficult to assess beyond this (Fig 1). After discussion with the neuroradiology team, this finding is consistent with subacute combined degeneration of the spinal cord, a condition most frequently seen in vitamin B_{12}, or cobalamin, deficiency. Although these findings are highly suggestive of B_{12} deficiency, the physician should consider a broader array of differential diagnoses such as inflammatory conditions (such as multiple sclerosis or acute disseminated encephalomyelitis), infectious myelitis, or atypical malignancy. Suspicion for alternate diagnoses should be based on additional supporting findings on history, examination, laboratory values, and imaging.

Dr Dowdell-Smith, how does this change your differential diagnosis, and what diagnoses concern you the most in a patient with these findings?

Dr Dowdell-Smith

Subacute combined degeneration was an unexpected finding in this patient. This appears on the MRI as a degeneration of the dorsal and lateral white matter of the spinal cord. Subacute degeneration of the spinal cord typically presents with ataxia, slowly evolving weakness, and sensory abnormalities[8]; the patient reported none of these signs or symptoms before her initial presentation with influenza. However, signs and symptoms became more apparent through the course of her hospitalization. Her MRI findings are highly characteristic of B_{12} deficiency. B_{12} deficiency may be due to decreased absorption of B_{12}, inability to properly use B_{12}, and, less likely in this case, exposure to a toxin, such as nitric oxide, that results in inactivation of B_{12}.[9]

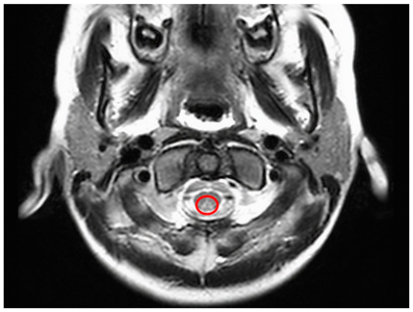

FIGURE 1
Axial T2 MRI image of the spine at the level of the dens. The red circle is highlighting the spinal cord with bilateral-symmetric increased signal intensity of the dorsal columns. This image was used with permission of the family and Texas Children's Hospital Department of Radiology.

Dr Cohen

Additional focused histories were obtained. It was discovered that the child had difficulty walking after exercise in school ~2 weeks before the onset of influenza. In addition, her diet was primarily restricted to simple carbohydrates, with a paucity of meats, poultry, legumes, and vegetables.

With her low BMI (first percentile z score -2.5), there was concern for possible malabsorption leading to vitamin deficiency. Gastroenterology was consulted and recommended additional screening laboratory tests for celiac disease as well as stool studies to evaluate for inflammation and malabsorption.

Screening thyroid testing revealed a low thyroid-stimulating hormone level of 0.3 μIU/mL (normal range 0.7–4) and a high-normal free thyroxine level of 1.8 ng/dL (normal range 0.8–2). Endocrinology was consulted for further guidance. A diagnosis of pernicious anemia and autoimmune polyglandular syndrome was considered given its association with both malabsorption and hyperthyroidism. However, further laboratory evaluation revealed negative results, and her laboratory tests were felt to be more consistent with sick euthyroid syndrome.

Despite the concern for B_{12}-related subacute combined degeneration of the spinal cord, B_{12} and folic acid levels returned normal.

Homocysteine and methylmalonic acid levels were pending.

A repeat complete blood count revealed a downtrend of the ANC of 296 cells per μL, a downtrend of the hemoglobin level of 11 g/dL (with a mean cell volume of 94 fL; age normal range 76–90), and a downtrend of the platelet count of 141×10^3/μL. Given the concern for inflammatory lesions in the spinal cord and new pancytopenia, oncology was consulted with concern for possible malignancy.

Dr Iacobas, how do you think through the differential diagnosis in a child with pancytopenia, and what special considerations are present in this case?

Dr Ionela Iacobas, Pediatric Hematologist and Oncologist

Pancytopenia during or immediately after a viral illness is common in pediatrics. Usually it is not a concerning sign, but extensive education is offered to the family, including neutropenic precautions and close monitoring by the hematologist or primary physician until the counts recover. In our case, the thrombocytopenia was minimal (141×10^3/μL; normal values would be $>150 \times 10^3$/μL), the neutropenia was severe (ANC reached 300×10^3/μL; normal values would be $>1500 \times 10^3$/μL), and the hemoglobin level was minimally decreased. Still, all of these numbers could have been explained by viral-induced bone marrow suppression.

In this case, the moderate macrocytosis of the red blood cells was unusual. In patients with normal hematopoiesis, the most common cause of macrocytosis is reticulocytosis.[10] Macrocytosis of red blood cells without a high reticulocyte count can be due to vitamin B_{12}, folate, vitamin B_1, or copper deficiency as well as medications, toxins, hypothyroidism, or myelodysplastic syndromes associated with trisomy 21. Our patient underwent extensive investigations to rule out the other possible causes.

As mentioned above, malignant processes were also on the differential, and the peripheral smear was analyzed multiple times during the admission for confirmation. No leukemic blasts or other malignant cells were reported. We considered bone marrow aspiration and biopsy, but when the homocysteine level resulted, the procedure was canceled and attention was turned completely toward a metabolic etiology.

Dr Cohen

Results of multiple studies returned negative, including folate level and viral studies for Epstein-Barr virus, cytomegalovirus, HIV, and parvovirus B19. The homocysteine level returned as >100 μmol/L. Dr Owolabi, how did you make sense of a normal B_{12} and folate level but a homocysteine level that was too high to be measured? What was your next step?

Dr Owolabi

On the basis of the clinical picture and imaging, it was presumed that there would be evidence of a B_{12} deficiency. Despite the normal B_{12} value, serum assays are a poor indicator of B_{12} deficiency because they do not correlate with tissue stores.[11] Intermediate amino acids, such as homocysteine and methylmalonic acid, are more useful because their metabolism is dependent on the presence of B_{12} and folate within the tissue.

Homocysteine levels can be elevated in both folate and B_{12} deficiency. However, the serum folate level was normal, and folate deficiency is not usually associated with neurologic changes or this patient's MRI findings. In contrast, an elevated methylmalonic acid level is indicative of B_{12} deficiency. At this point, confirming elevation of the serum methylmalonic acid level was thought to be the next step in solidifying the diagnosis.

The patient had a restrictive diet that put her at risk for B_{12} deficiency, but insufficient dietary intake of B_{12} is rare in children.[12] Given the patient's age and the acuity of the presenting symptoms, we were also concerned about a metabolic cause for her symptomatology.

Dr Cohen

Dr Laufman, most commonly, we worry about metabolic diseases presenting catastrophically in infancy, but this child presented with symptoms concerning for a metabolic disease in late childhood. When should we be concerned about a metabolic disease in older children? How do you make sense of this patient with disparate laboratory values?

Dr Jason Laufman, Pediatric Genetics Fellow

Many rightly suspect an IEM in the infant with lethargy, poor feeding, acidosis, or hyperammonemia. However, IEMs may present with a wide array of signs and symptoms, and a number of these conditions are not included on the newborn screen (NBS). The NBS identifies many metabolic conditions with high morbidity and/or mortality, but other metabolic diseases may not present until later in life either because of the natural history the condition or because of a milder presentation of a classically severe condition. Unfortunately, there are no objective standards for when to evaluate for an IEM. Generally, a clinician should consider IEMs in patients who have abnormal and unexpected data on routine laboratory tests or imaging, especially combined with unusual or unexplained findings on history or examination. Moreover, the index of suspicion should be high in children born outside of the United States. Each country's, or even each region's, NBS program, including economical

support and technologies used, varies widely and is rapidly changing.[13] It can often be difficult or time consuming to track down an international NBS or even accurately determine which diseases are screened for.

In the case of disorders of intracellular metabolism of vitamin B_{12} (cobalamin), presentation can be any time from in utero to adulthood. Cobalamin undergoes endocytosis and multiple modifications, all which can be affected by IEMs. It is vital for the conversion of homocysteine to methionine as well as methylmalonyl–coenzyme A (CoA) to succinyl-CoA (Fig 2). Depending on the particular enzyme involved, patients with disorders of intracellular cobalamin metabolism can have elevated homocysteine levels with low methionine and/or elevated methylmalonic acid levels. Cobalamin C deficiency, the most common error of cobalamin metabolism, is often detected on NBS with elevated C3 levels on tandem mass spectrometry, but other disorders of intracellular cobalamin metabolism may not be evident on NBS.[14] Younger patients can present with poor feeding, encephalopathy, developmental delay, seizures, and poor growth. Older individuals can present with neuropsychiatric symptoms, cytopenias (including megaloblastic anemias with normal B_{12} and folate levels), thrombosis (including stroke), and subacute combined degeneration of the spinal cord.[15] In this case, a disorder of intracellular cobalamin metabolism was correctly suspected on the basis of the radiographic findings of subacute degeneration of the spinal cord with normal B_{12} levels and elevated homocysteine levels.

Dr Cohen

The methylmalonic acid level returned elevated to 57.1 μmol/L (normal range 0–0.5 μmol/L). Other metabolic testing results, such as plasma amino acids, urine organic acids, and the acylcarnitine profile, were normal. After treatment with intramuscular B_{12} and betaine, the homocysteine level normalized, and she began to have improved lower-extremity strength and reflexes but continued to have an ataxic gait. Because of persistent difficulty with ambulation, proprioception, and activities of daily living, she was discharged to a pediatric rehabilitation unit. With intensive rehabilitation, she was able to improve her functional status, walking partially independently and partially with the help of a walker, with improved energy and resolution of all pain. She continued to have impaired proprioception but otherwise was neurologically intact.

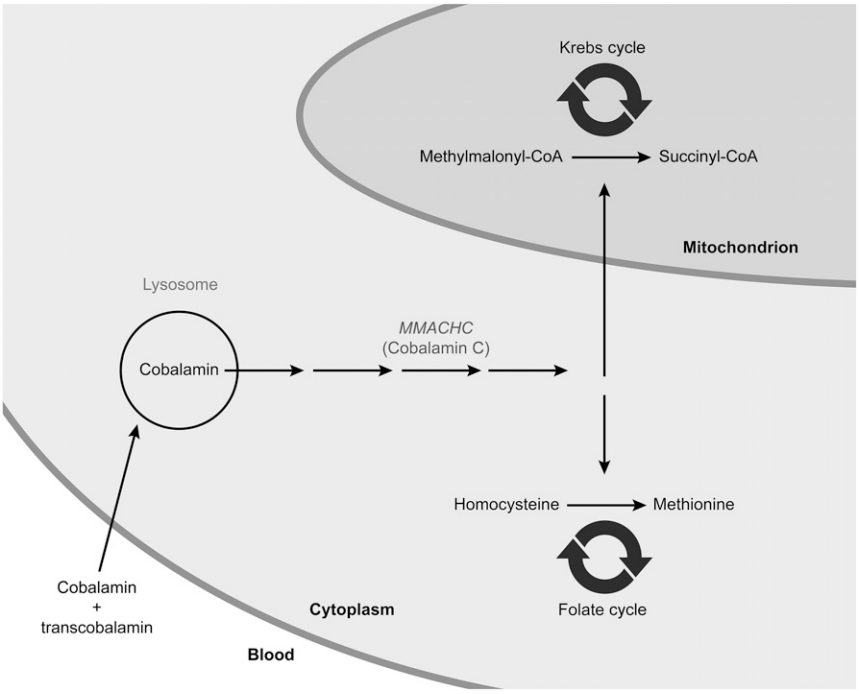

FIGURE 2

Intracellular cobalamin metabolism begins with endocytosis of cobalamin and transcobalamin. Transcobalamin is removed within the lysosome. Cobalamin then undergoes multiple reductions before aiding in the conversion of homocysteine to methionine and methylmalonyl-CoA to succinyl-CoA. Errors along this pathway may cause elevation of homocysteine and/or methylmalonic acid.

FINAL THOUGHTS AND DISCUSSION

Dr Cohen

In the initial evaluation of this patient, her symptoms were attributed to the diagnosis of influenza infection, a common cause of myalgias and generalized weakness in children. However, as her course evolved and her influenza symptoms improved, her lower-extremity examination became progressively more striking. Clues about her underlying diagnosis became more apparent later in her clinical course, including a history of difficulty walking preceding the symptoms of influenza and an examination more consistent with coordination deficits than weakness. This history helped this multidisciplinary team to follow a logical and stepwise approach in the evaluation and diagnosis of the child's condition.

After the complete evaluation by genetics, a cobalamin metabolism disorders panel was sent, and 1 heterozygous pathogenic variant and 1 heterozygous, likely pathogenic variant in the *MMACHC* gene were found. The pathogenic variant is

associated with methylmalonic aciduria and homocystinuria (cb1C type), the most common inborn error of cobalamin metabolism.

Dr Laufman

IEMs can present in diverse and unexpected ways. As such, the clinician must maintain a high level of suspicion in cases in which the signs and symptoms do not fit a classic presentation of disease. In this case, an IEM was appropriately suspected and supported with biochemical screening laboratory tests, including an acylcarnitine profile and total plasma homocysteine, plasma methylmalonic acid, and urine organic acid levels.

Definitive diagnosis of an IEM is achieved with molecular genetic testing. Identification of specific IEMs is important for initiating therapies to slow progression, prevent intermittent decompensations, guide appropriate medical screening, or, in this case, reverse symptoms of the disease. Additionally, identification of IEMs can facilitate screening of other family members who may be at risk and allow for early treatment before manifestation of the disease. Our patient's asymptomatic brother underwent screening and was found to have elevated homocysteine levels. Molecular confirmation of his diagnosis is pending, but he has been started on hydroxycobalamin.

In the cases of disorders of intracellular cobalamin metabolism, the mainstay of therapy is parenteral administration of hydroxycobalamin, which has been shown to be more effective than other formulations, including oral hydroxycobalamin. For disorders with hyperhomocysteinemia, such as cobalamin C deficiency, we may consider the use of betaine to convert homocysteine into methionine.[15]

CONCLUSIONS

The case of this young girl stresses the importance of recognizing and pursuing significant findings when they are not consistent with the presumed diagnosis. In this case, the progressive lower-extremity and gait abnormalities were inconsistent with her improving influenza symptoms, prompting further careful evaluation and imaging. Vitamin B_{12} deficiency should be included within the differential of a child presenting with abnormalities of gait and lower-extremity proprioception, especially in children with abnormal diets, malabsorption, or cytopenias.

ACKNOWLEDGMENT

We thank Dr Huy Tran, MD (neuroradiologist at Baylor College of Medicine and Texas Children's Hospital), for helping us review and prepare the MRI images of the patient.

ABBREVIATIONS

ANC: absolute neutrophil count
CoA: coenzyme A
ED: emergency department
IEM: inborn error of metabolism
NBS: newborn screen

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Pediatrics originally published online March 6, 2020;

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