"Plateaus Aren't Just for Climbers" Vitamin Deficiency Post-Stroke Presenting as Fatigue and Cryptogenic Rash

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Abstract

In the stroke recovery period, patients will often struggle with post-stroke depression, post-stroke spasticity, and can suffer from post-stroke fatigue. The recommended workup for post-stroke fatigue centers around identifying contributing factors including pain, medication side effects, and/or anxiety/depression. Nevertheless, one of the major tests ordered in recovery from many neurologic diseases is often overlooked - screening for vitamin deficiencies. Vitamin deficiencies are highly prevalent in patients post stroke, especially deficiencies of the B vitamins and vitamin D. Even in the absence of post-stroke dysphagia, stroke patients have lower blood concentrations of multiple vitamins compared to healthy subjects. Herein, we describe an illustrative case report of a patient who developed pellagra post-stroke, which led to her slowed recovery and the steps taken for diagnosis.

Keywords: Stroke, pellagra, vitamin deficiencies, post-stroke recovery

Background

Post-stroke fatigue is a common and debilitating symptom, affecting between 42 to 53% of stroke survivors.[1] The recommended workup for post-stroke fatigue centers around identifying contributing factors such as depression, anxiety, sleep disturbances, pain, and medication side effects.[2] Screening for vitamin deficiencies is not routine, which can be an overlooked cause of impaired stroke recovery. Vitamin deficiencies are highly prevalent in patients post stroke, especially deficiencies of the B vitamins and vitamin D. Even in the absence of post-stroke dysphagia, stroke patients have lower blood concentrations of multiple vitamins compared to healthy subjects.[3]

B-vitamins are important for neurologic function, and deficiencies may result in peripheral neuropathy, cognitive impairment, and neuropsychiatric symptoms.[4] Pellagra refers to a severe cellular deficiency of niacin (B3) classically presenting with a triad of

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dermatitis, diarrhea and dementia.[5] The dermatitis is typically a bilaterally symmetrical, well-demarcated eruption at sites exposed to sunlight or pressure, initially bright red and later becoming dark and scaly. Other manifestations of pellagra include fatigue, weakness, poor appetite, anxiety, and irritability, which eventually progresses to encephalopathy and multiorgan failure if untreated.

Thiamine (B1) deficiency, folate (B9) deficiency, and cyanocobalamin (B12) deficiency are prevalent in the setting of stroke recovery, across multiple studies.[6-9] All these vitamins are important in stroke recovery. B1 vitamins are important for carbohydrate metabolism and antioxidant properties.[10] Niacin (B3) is also a metabolic coenzyme and promotes phagocytosis of myelin debris.[11] B9 is crucial for DNA synthesis and tissue growth, differentiation, and repair.[4] Low B9 and elevated methylmalonic acid may predict long term cognitive impairment in stroke survivors.[6] Pyridoxal phosphate (B6) protects against excitotoxicity, and B12 promotes neuronal survival and remyelination.[10] In the post-stroke period, B12 deficiency delays motor function recovery and increases apoptosis in ischemic brain tissue.[8,9]

Here we present a continuation of a case report of a woman with a pontine hemorrhage treated with cavernous malformation resection a year prior,[12] now presenting with increased fatigue and plateau in recovery from her right hemiplegia. This report highlights the importance of nutritional deficiencies, focusing on measurement of serum B vitamins and vitamin D levels as part of post-stroke fatigue workup.

Case Presentation

A 24-year-old female with history of generalized anxiety disorder and pontine hemorrhage secondary to cavernous malformation underwent resection for definitive management, and recovered well in rehabilitation.[12] During her hospital stay she had been evaluated with MRI, started on a 3% saline drip to prevent edema within the infratentorial space, and eventually was discharged to rehabilitation with post-stroke symptoms of hemiplegia, hemiparesis, dysarthria, and spasticity. She improved significantly with physical therapy (PT) and occupational therapy (OT) over the first 6 months after resection, but improved only minimally over the next 6 months despite continued therapy. Furthermore, she developed low energy levels as well as mood swings, irritability, and impulsive behavior. One year later, she presents to her primary care physician (PCP) for follow-up endorsing fatigue, rash, plateauing in PT/OT, and mood swings.

During her PCP visit, she was noticed to have a rash on sun exposed areas of her skin which started about 7 months after the stroke. The patient described a transient, morbilliform/ erythematous eruption with blotchy morphology that fluctuated in intensity, persisting intermittently over multiple two-week periods before spontaneously resolving. The rash was red with well-demarcated borders and appeared bilaterally in sun-exposed areas including the patient's

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shoulder, arms, dorsal hand, and thighs (Figure 1). Autoimmune serologies were

Figure 1: Rash on Sun Exposed Areas

negative, and a coccidiomycosis test returned one positive result which infectious disease deemed a false positive. Finally, an allergy and immunology workup was also non-revealing for rash etiology.

During her neurology office visit, physical examination showed resolution of her post-stroke dysarthria. Remaining motor deficits included 4+ right grip strength, 3+ deep tendon reflexes throughout the right side, and a right-sided limp with ambulation.

Differential Diagnosis

In a patient who suffered from hemorrhagic stroke, potential causes for increased fatigue include post-stroke fatigue, metabolic disease, vitamin deficiencies, anxiety/ depression, medication adverse effects, and sleep disorders. The patient denied sleep related issues including witnessed apneas, snoring, or weight gain and physical examination did not support sleep study testing with a STOP-BANG score of 1 for daytime sleepiness. Complete blood counts (CBC) and complete metabolic panels (CMP) were unremarkable, rendering metabolic disease less likely. While the patient did have a known diagnosis of anxiety, this was under treatment and therefore deemed to be a less likely cause of her symptoms. The patient's medications were reviewed and the two medications, hydroxyzine 50 mg taken as needed and sertraline 50 mg taken daily were very unlikely to cause these symptoms especially as they had been in use for years pre-stroke. Post-stroke fatigue was also deemed less likely because she had not experienced fatigue earlier in recovery. Importantly, none of the proposed differential diagnoses appropriately explained the rash.

Laboratory Work-Up

Serum B1, B9, and B12 levels and a vitamin D-OH25 level were obtained. Vitamin B1 level was low at 66 nnmol/L (normal range

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78-185 nnmol/L). Vitamin D-OH25 was low for a person with a diagnosis of anxiety at 44.6 ng/mL (Normal range 50 ng/mL – 100 ng/mL for those with anxiety disorders).[12] Vitamin B9 was within normal limits at 7.8 ng/mL (Normal range greater than 4.0 ng/mL), and vitamin B12 was within normal limits at 632 pg/mL (Normal range 232 – 1245 pg/mL).

Given her low B1 level, serum B2, B3, B5, and B6 levels were obtained. B3 level was undetectable. B2 level was within normal limits at 11.0 nmol/L (normal range 6.2 – 39 nmol/L), B5 level was within normal limits at less than 40 ng/mL, and B6 level was within normal limits at 11.4 ng/mL (normal range 2.1 - 21.7 ng/mL).

Final Diagnosis and Treatment

The patient was started on vitamin B1 100 mg daily, B3 500 mg daily, and D3 125 mcg daily, subsequently noting far less fatigue, and after about 6 months of B3 supplementation, her rash resolved, suggesting the diagnosis of pellagra – a nutritional deficiency disorder rarely seen in the United States. Retesting vitamin B1, vitamin B3, and vitamin D-OH25 at the 6-month mark demonstrated total resolution of the deficiencies that had been discovered during her initial work up. Further work up with her PCP and with gastroenterology is currently ongoing.

Discussion

We present here a young hemorrhagic stroke survivor exhibiting stalled recovery of motor function and symptoms of pellagra months after the stroke, who was found to have deficiencies in vitamins B1, B3, and D. The patient's stroke presentation and immediate evaluation and treatment were described previously.[12] The continued development of this case demonstrates that a plateau in recovery and persistent fatigue post stroke warrant evaluation for vitamin deficiencies, even if dysphagia and malnutrition are not of concern.

Blood-based niacin assays can be unreliable, and urinary metabolites (N-methyl-nicotinamide and its 2-pyridone derivative) are the preferred biomarkers.[13] However, in this case the patient was exhibiting multiple signs of pellagra and had concomitant deficiencies in other B vitamins, which made the diagnosis of pellagra highly likely especially in the context of a negative work up for more probable causes of her disease state. Thus, immediate B3 supplementation was started since it would have been unwise to delay treatment. Additionally, her clinical response with total resolution of rash and other symptoms demonstrates that this was the final diagnosis. However, in cases where clinical suspicion is low, confirmatory testing with urinary metabolites is frequently warranted. Additional work-up for pellagra should include evaluation for underlying etiologies, such as alcohol use disorder, medications, colitis, and carcinoid tumor.[5]

Many clinical studies have investigated the potential benefits of vitamin supplementation in preventing stroke,[14,15] but few have explored the role of B vitamin supplementation in aiding post-stroke recovery or the importance of screening for vitamin deficiencies during this period. The B vitamins are implicated in neuroplasticity,

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and it follows that these vitamins play a crucial role in stroke recovery when ischemic brain tissue is undergoing repair.[16,17] Mechanistically, the vitamin B3 subtype nicotinamide enhances remyelination and reduces inflammation by altering the phenotype of astrocytes and microglia.[18,19] Vitamin B12 is involved in remyelination, while B1 facilitates carbohydrate use for energy in regenerating brain tissue.[10] Our patient presented a year after her stroke with decreased vitamin B1 and undetectable vitamin B3, possibly due to consumption of these micronutrients in neurologic repair with subsequent slowing of recovery.

These vitamin levels are not often tested during routine stroke follow up. However, a retrospective study found the prevalence of frank vitamin B1 deficiency to be 14% among stroke patients in rehabilitation, while a cross-sectional study found that 51% of elderly stroke survivors had folate deficiency at 20 months post stroke.[6,7] Other common deficiencies that develop post stroke include vitamin E, docosahexaenoic acid, eicosapentaenoic acid, vitamin C, selenium, and vitamin D.[20,21] The potential mechanism behind the development of B-vitamin and other essential nutrient deficiencies post stroke is potentially related to an increase in the amount of one carbon metabolism which is upregulated in damaged brain tissue.[22] This process requires the use of a number of vitamin cofactors including zinc, vitamin B1, vitamin B2, vitamin B6, vitamin B9, and vitamin B12.

With regard to supplementation post stroke, one prospective study demonstrated a positive association between vitamin B12 levels and functional recovery at 3 and 6 months post stroke.[23] However, previous studies on post stroke vitamin supplementation have yielded mixed results. Two randomized controlled trials found no benefit of daily B vitamin supplementation on post stroke cognitive and neuropsychiatric sequelae or on the progression of ischemic brain lesions except in a subgroup of patients with severe cerebral small vessel disease.[24, 25] In another trial, supplementation with B vitamins plus omega-3 fatty acids helped preserve temporal orientation ability in patients with prior stroke.[26] The literature on vitamin D supplementation following stroke is more robust but also yields inconsistent findings, with some studies showing improvement in functional outcomes and fatigue especially in patients with already low vitamin D levels,[27-29] and others suggesting no effect on motor and psychological outcomes.[30,31] For our patient, treatment with vitamins D, B1, and B3 resulted in resolution of her fatigue and pellagra-related rash. Thus, while universal vitamin supplementation in stroke patients is not currently indicated, supplementation can be beneficial when targeted to address known vitamin deficiencies.

Conclusions

Our case highlights that routine screening for vitamin deficiencies should be considered in patients with unexplained fatigue, rash, or plateaued stroke recovery. Vitamin deficiency is a common and easily treated cause of these symptoms. Future prospective studies should further evaluate the effects of universal vitamin screening and supplementation, as well as explore which

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subpopulations of post stroke patients receive the greatest benefit from such monitoring and treatment.

Conflicts of Interest

The authors report no conflicts of interest.

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