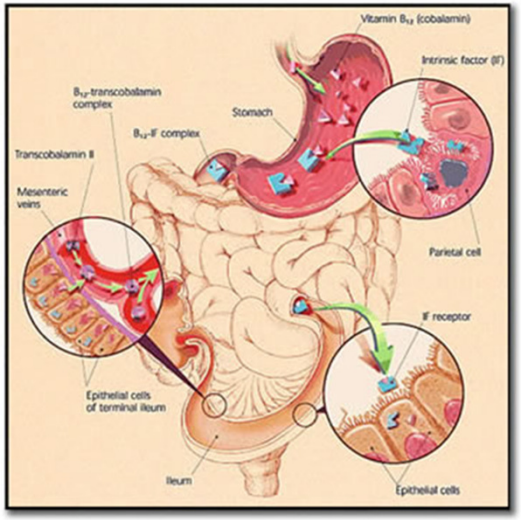
Subacute Combined Degeneration Myeloneuropathy

November 14, 2020

Vitamin B_{12} Deficiency

Patients with vitamin B12 deficiency present with a wide spectrum of manifestations

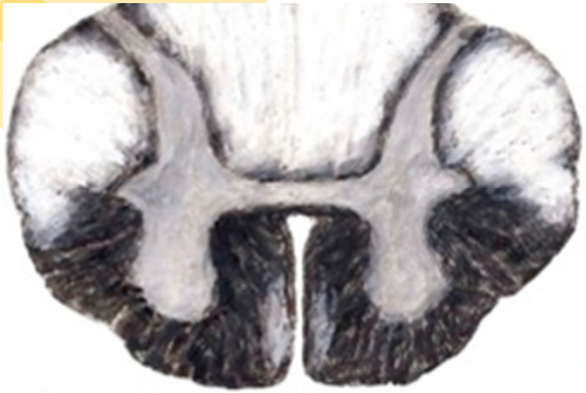


The acidic environment of the stomach

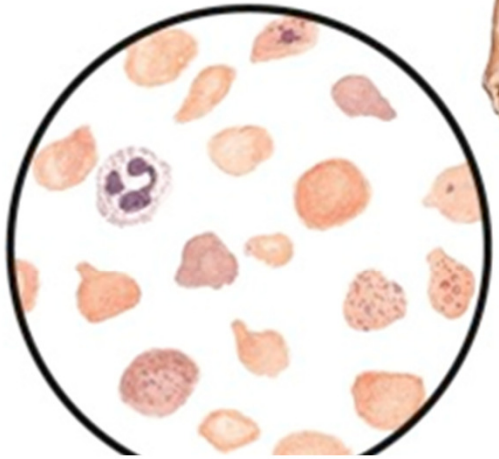
facilitates the breakdown of vitamin B-12 that is bound to food, while intrinsic factor, which is released by parietal cells in the stomach, binds to vitamin B-12 in the duodenum.

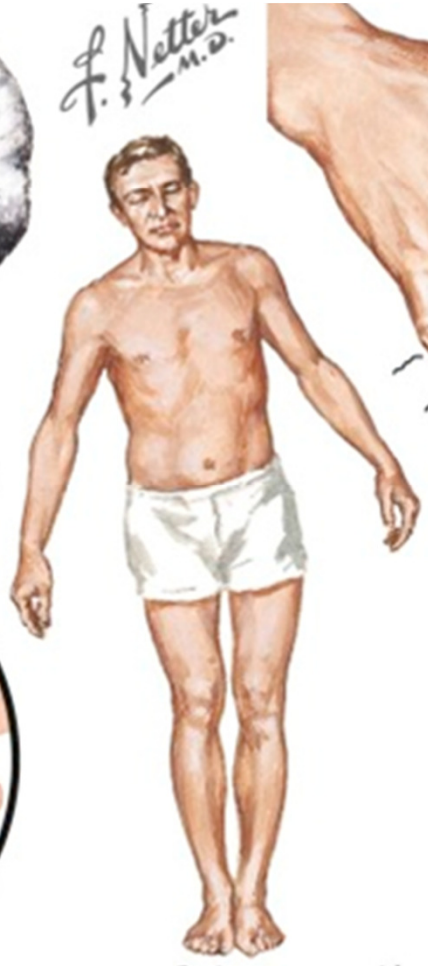
This vitamin B-12-intrinsic factor complex subsequently aids in the absorption of vitamin B-12 in the terminal ileum.

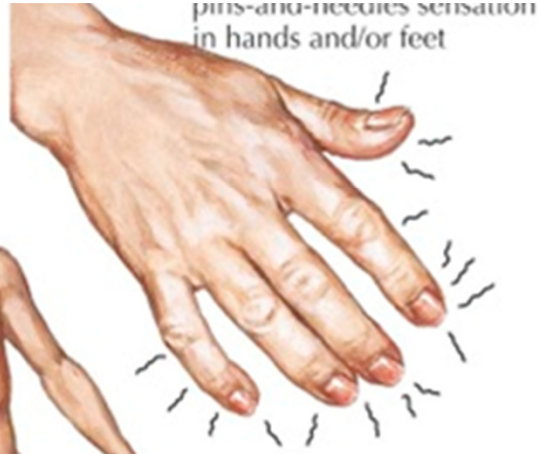
- *A defect in any of these steps can put patients at-risk or lead to deficiency.*



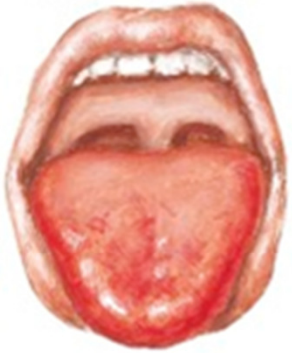
Degeneration of posterior columns, and corticospinal and direct spinocerebellar tracts, chiefly in midthoracic spinal cord





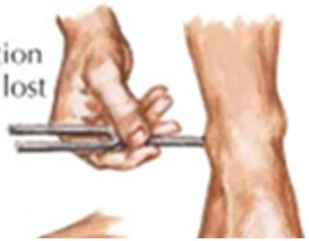


Glossitis common



Ataxia, especially in darkness

Vibration sense lost



Position sense lost

Which of the following symptoms is NOT a manifestations of B12 deficiency?

- ***Impotence***
- ***Incontinence***
- ***Fatigue***
- ***Weakness***
- ***Vertigo***
- ***Dementia***
- ***Depression***
- ***Memory loss***
- ***Ataxia***
- ***Abnormal gait***
- ***Peripheral neuropathy/pain in extremities***
- ***Anemia***
- ***Leukopenia***
- ***Thrombocytopenia***

If you selected "vertigo" then you are correct.

Numerous citations within the literature support the wide spectrum of clinical manifestations that may be exhibited by patients with B-12 deficiency.

The entire list, with the exception of the above, may be observed, thus complicating the diagnosis.

Recently, a case study was published in "Neurology India" reporting a 55 year old man with Parkinson's-like symptoms responding to B-12 therapy.

Diagnosis of B-12 deficiency is typically based on measurement of serum B-12 levels.

What percentage of patients with sub-clinical disease may have normal B-12 levels?

- 20%
- 30%
- 40%
- 50%

The correct answer is D.

Data suggest that about 50% of patients with sub-clinical disease may have normal B-12 levels.

That is why a more sensitive method of screening for B-12 deficiency is the measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B-12 deficiency.

According to recent epidemiologic reports, what percentage of the general population is considered to be deficient in vitamin B-12?

Up to 5%

Up to 10%

Up to 15%

Over 15%

Correct Answer : D.

Studies have reported varying incidence rates, however, most agree that cobalamin deficiency occurs in three to 40% of the general population.

In one study, 15% of adults older than 65 years had laboratory evidence of vitamin B-12 deficiency.

Which of the following patients do you believe to be "at-risk" for B-12 deficiency?
Patients with: Which of the following patients do you believe to be "at-risk" for B-12 deficiency?
Patients with:

(Check all that Apply)

- *Autoimmune disease*
- *Crohn's disease*
- *Malabsorption syndromes*
- *HIV infections*
- *Multiple Sclerosis*
- *Strict vegan diets*
- *Gastric disorders requiring histamine receptor agonists or proton pump inhibitors*
- *Advanced age, over 65*

If you checked ALL of the boxes, then you understand how widespread this condition may potentially become.

Also, an understanding of the vitamin B-12 absorption cycle helps illuminate the potential causes of deficiency.

Studies have shown that the absorption of vitamin B-12 from food is complex and that defects in any of the absorption steps can lead to deficiency.

True or False:

True

False

Correct answer : True

This is a true statement, in fact, an understanding of the vitamin B-12 absorption cycle helps illuminate the potential causes of deficiency.

The acidic environment of the stomach facilitates the breakdown of vitamin B12 that is bound to food.

Intrinsic factor, which is released by parietal cells in the stomach, binds to vitamin B12 in the duodenum.

This vitamin B-12 intrinsic factor complex subsequently aids in the absorption of vitamin B-12 in the terminal ileum.

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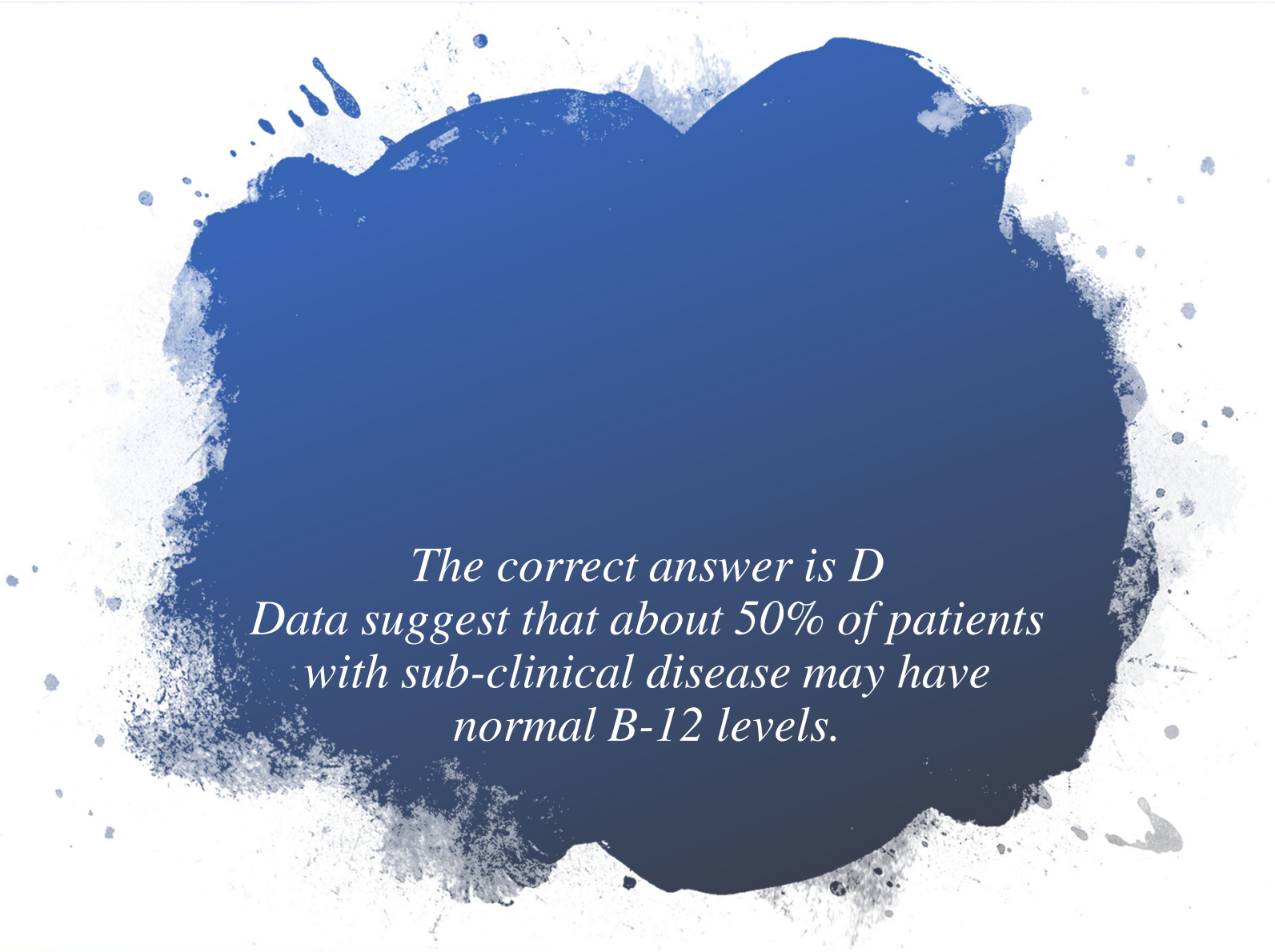
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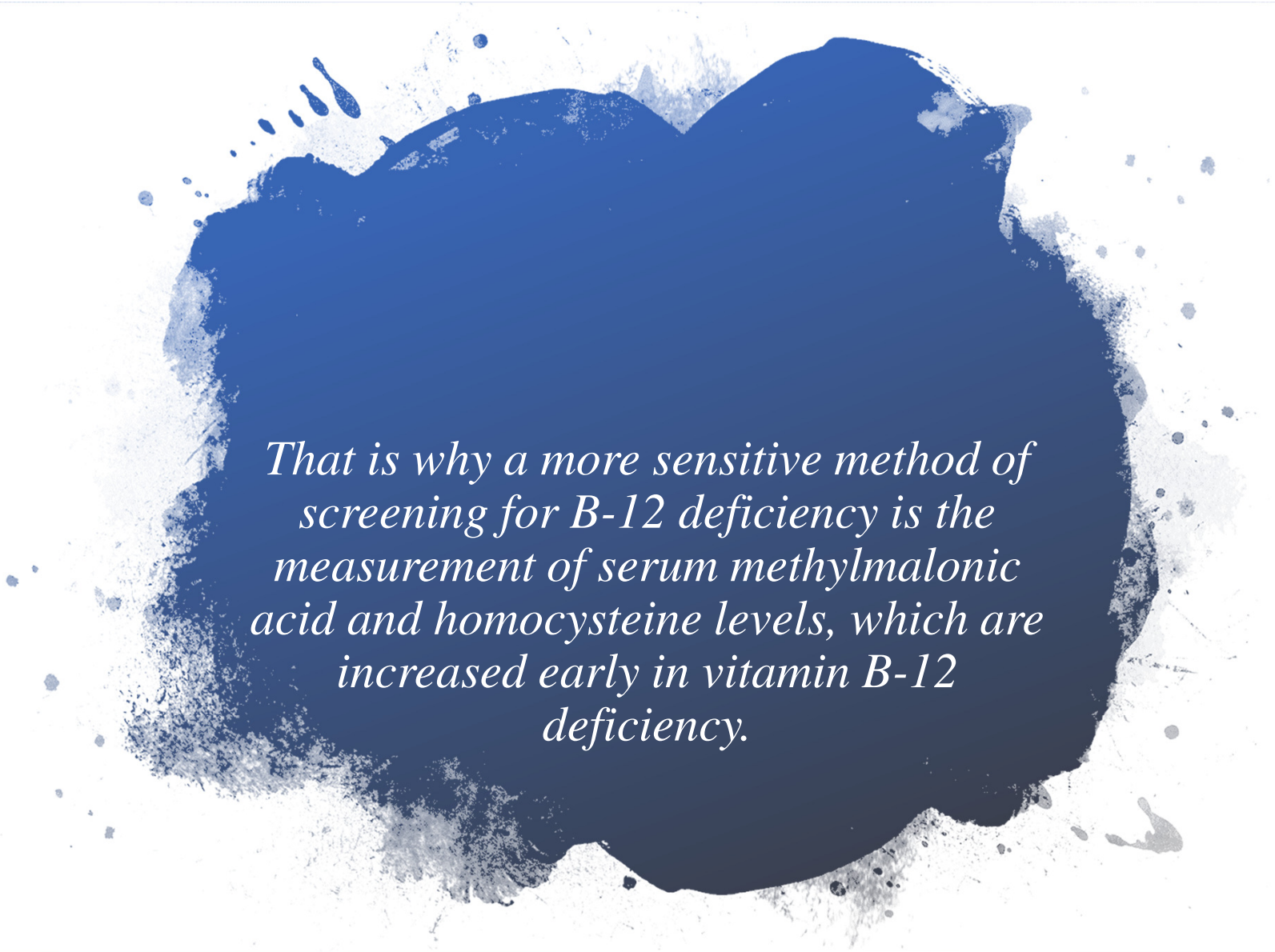
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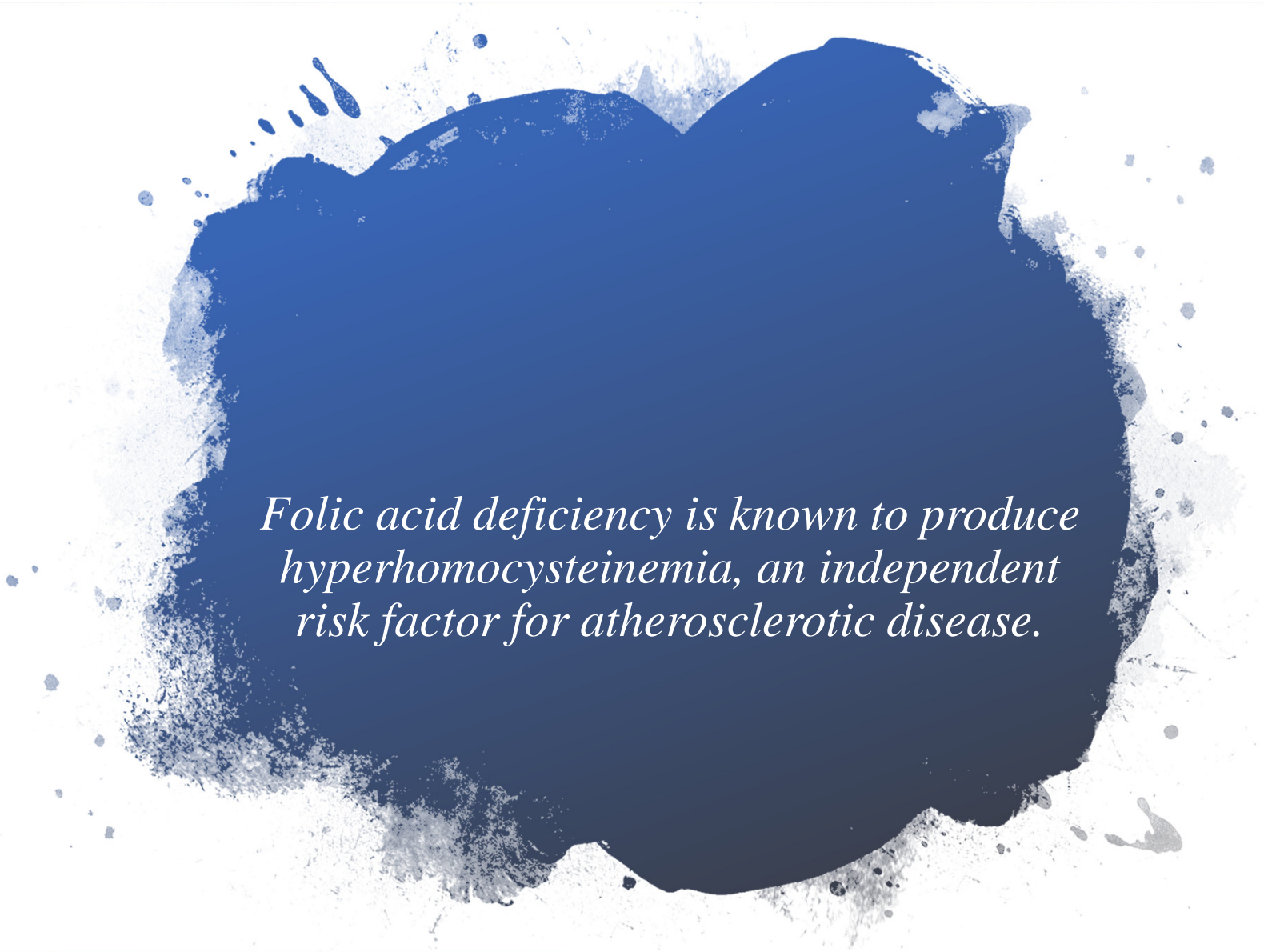

Folic acid deficiency is known to produce hyperhomocysteinemia, an independent risk factor for atherosclerotic disease.

A deficiency in what other vitamin may also lead to hyperhomocysteinemia?

B-12
Riboflavin
Vitamin C
Vitamin

Correct Answer : A

Vitamin B-12 deficiency also produces hyperhomocysteinemia.

Correct Answer : A

Although the role of folic acid supplementation in reducing homocysteine levels as a method for preventing coronary artery disease and stroke continues to be a subject of great interest,

there has been little emphasis on the potential role of vitamin B-12 deficiency as a contributing factor in the development of cardiovascular disease.


Case 1
November 6, 2020

SM is a 22-year-old female

who presents to ECMC ED a week ago with worsening leg weakness and numbness, reports history of low back pain, bilateral leg weakness, radicular pain and foot drop since her MVA in June 2020.

She started requiring a cane and/or walker in August 2020.

She had a couple episodes of nocturia within the last month.

ED

Her symptoms significantly worsened after a mechanical fall at a store 4 days ago.

She denies closed head injury or loss of consciousness.

Over the last 3 days, she has not been able to ambulate and is dragging herself across the room.

ED

She was also experiencing weakness, tingling and cramping of her hands bilaterally.

Back pain also worsens when she flexes her neck.

ED

She contacted her neurosurgeon who suggested coming to the ED to rule out Guillain Barre.

In ED CSF with normal protein and no evidence of infection.

Next day patient was interviewed and examined after reviewing the available record,

Accident according to the patient happened while she was driving and she may have been sleepy.

She had MRI of the Brain spine, cervical thoracic and lumbar showed no obvious abnormality.

History

She describes weakness of the legs and clumsiness of the hands,

Lhermitte phenomenon, neck discomfort, lower back pain, heaviness and tightness of the chest down.

She has some bladder urgency frequency and incontinence.

No visual disturbances diplopia or monocular blindness.

On examination

She is alert and oriented, fluent coherent and cooperative with no dysarthria and no dysphasia, hypo-or hyperkinesia, tremor or dyskinesia.

Head is atraumatic and ENT unremarkable. ***She has Lhermitte sign.***

Cranial N: *Pupils are 2 mm reactive or around, no anisocoria or ptosis, ophthalmoplegia or nystagmus, facial asymmetry but she has* ***some hearing deficit.***

On examination
Upper extremity:

Strength 4/5 proximally, 3/5 distally with poor grip and weakness of the small hand muscle.

Distal sensory loss in the stocking distribution.

No Hoffmann sign or finger jerk.

She has sensory level on the upper trunk with hyperesthesia.

Lower extremity

Strength 3-4/5 proximal and 2–3/5 distally with bilateral partial foot drop.

Reflexes are normal upper extremity and knee jerk 2+ but and ankle jerks are absent.

She has no obvious Babinski sign, or clonus.

On examination

She has distal sensory loss in a stocking distribution.

Gait and Romberg could not be examined because of the weakness.

CSF

Clear and colorless
Glucose 74, protein 35,
1 WBC, 614 Rbc

Acute on chronic BLE weakness and numbness.

Initial onset after MVA in June 2020, significant worsening of symptoms after a fall 4 days

Abnormal neurologic exam.

Unlikely GBS with hyperreflexia and normal CSF protein.

Exam findings may be mixed, including myelopathy and peripheral neuropathy.

Repeat imaging recommended to rule out compression of spinal cord from disc.

Would consider vitamin B12 deficiency in setting of Crohn's.

Can start IM injections now while waiting for blood work.

Assessment:

The clinical presentation and the findings suggest subacute neuropathy as well as myelopathy (Lhermitte and sensory level and having high MCV and Crohn's disease with malabsorption syndrome, could be compatible with subacute combined degeneration of B12 deficiency.

Recommendation:

We should obtain B12 level, folic acid level,TSH, free T4, T3, thyroid antibodies, ESR, CRP and methylmalonic acid level, etc and major emphasis on her GI disturbances.

Recommendation:

major emphasis on her GI disturbances.

Recommendations:

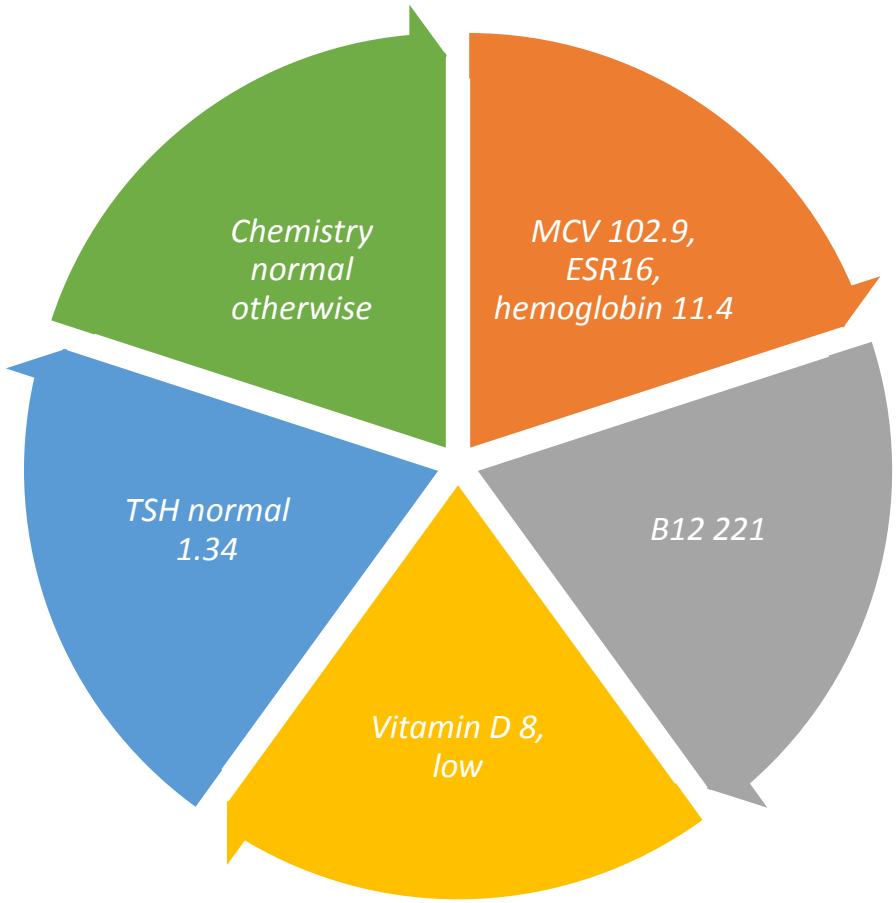
Start vitamin B12 1000 mcg IM injections daily

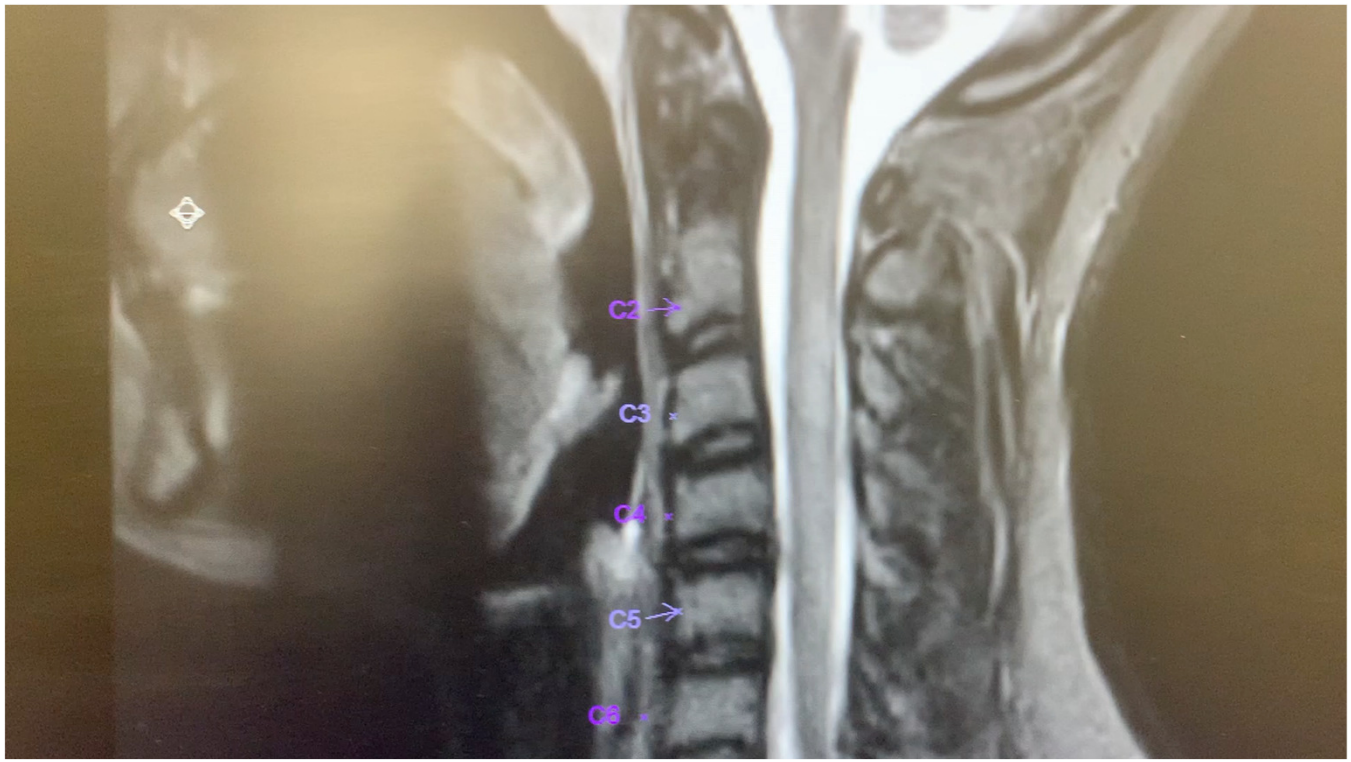
MRI cervical, thoracic and lumbar spine because of the MVA to exclude compressive process, disc

Continue gabapentin, baclofen

PT/OT

Laboratory data

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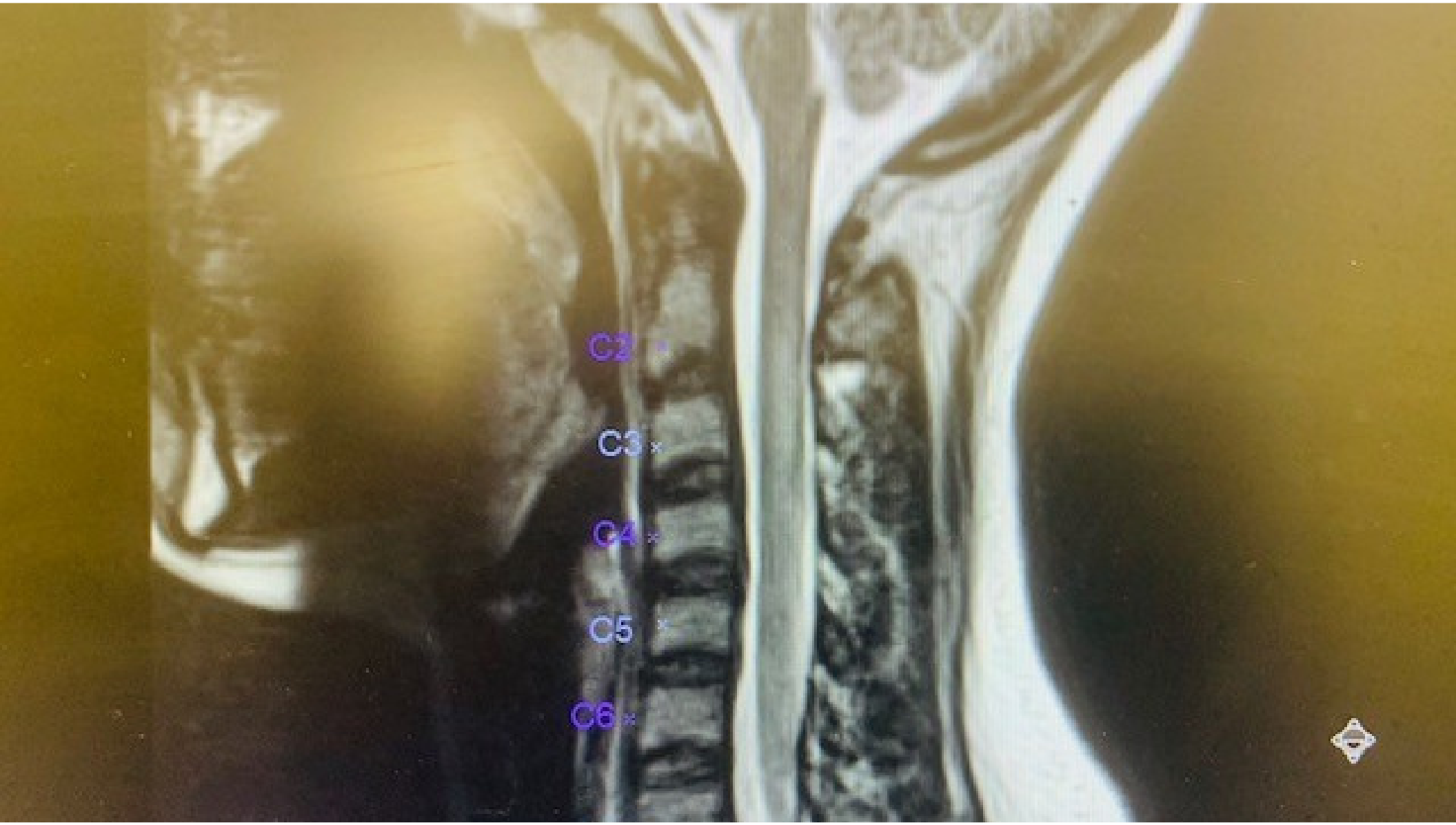
C2
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T2 hyperintense intramedullary

Diffuse, symmetric, T2 hyperintense intramedullary signal involving the dorsal columns of the cervical cord and to lesser extent within the thoracic cord.

These findings can be seen with subacute combined degeneration (vitamin B12 deficiency), vitamin E deficiency, copper deficiency, or nitrous oxide toxicity.

Other etiologies, such as demyelination or infectious/inflammatory process are also possible.


Questions /Discussion


Case 2

February 6, 2006

a 70 year old right handed man, diabetic, hypertensive, presents for further neurological evaluation because of lightheadedness and dizziness, been off balance, and incoordinated, and falling tendency.

He fell once while he painting, became dizzy and lost his balance.

Cranial CT scan, and Carotid Doppler show no major abnormality.

He denies having TIA, stroke, syncope or seizure disorder, in the past.

PAST MEDICAL HISTORY:

hypertension, diabetes, in past was hit by a car, and has rods in left lower extremity,

CURRENT MEDICATIONS: Aspirin, Glyburide, Lisinopril, Lescol

SOCIAL HISTORY: married, retired electrician, nonsmoker, nondrinker, with no IV drug use

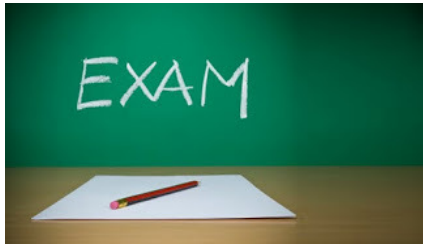
DRUG ALLERGY: He has no known drug allergy.

SYSTEM REVIEW: no systemic or neuropsychiatric

he stands about 5’9 feet, and weighs about 230 pounds, and his vital signs are normal,

deep reflexes are sluggish upper extremities.

He has distal sensory impairment in stocking distribution.



Clinical assessment

His symptomatology is consistent with peripheral neuropathy,

March 28, 2006

Presents for further follow-up evaluation, this time he reports and complains of discomfort, and funny feeling down his upper extremities when he bends his neck.

He denies having neck pain and back pain discomfort, no problem with bowel or bladder control. he denies having visual disturbance, diplopia or monoocular blindness and has no other new symptoms.

PHYSICAL EXAMINATION:

He is a pleasant man, alert, oriented, fluent, coherent and cooperative, with no apparent dysarthria, or dysphasia, no arm lag, or pronator drift, ataxia, or weakness.

The neck is supple with limited range of motion, and Lhermitte sign.

He has no spasticity, or rigidity.

He has vibratory loss in lower extremities.

The cardiovascular and pulmonary examinations are normal, the remainder of examination is unchanged otherwise.

February 22, 2006

CMP Normal glucose 71, BUN 27.4, Creat 1.2

CBC: ***Hb 10.6, WBC 2.81, MCV 106.9, Plat 181***

ESR 14

Free T4 1.55

B12: 89 PG/ML

Folate more than 24 NG/ML

CLINICAL ASSESSMENT & PLAN:

Myelopathy , peripheral neuropathy, secondary to B12 deficiency.

For further evaluation obtain MRI of the cervical spine rule out cervical disc herniation, spondylosis, or spinal stenosis.

Patient placed on more B12 replacement therapy.

Vitamin deficiency related to inadequate intake or absorption of cobalamin (vitamin B_{12})

Cobalamin is critical for CNS myelination and normal functioning.

Deficiency can cause a multitude of symptoms and disorders including megaloblastic anemia, bone marrow dysfunction, and diverse and potentially irreversible neuropsychiatric changes.

Myeloneuropathies

Disorders that concomitantly affect the spinal cord and peripheral nerves can be characterized as myeloneuropathies

Such conditions can be broadly categorized as

- *Metabolic*
- *Inflammatory*
- *Infectious*
- *Hereditary disorders*

Diagnostic Approach to Myeloneuropathy

Because these disorders may present with predominantly myelopathic or peripheral neuropathic signs and symptoms,

a careful neurologic examination and a thoughtful diagnostic evaluation are necessary to establish a diagnosis

A thoughtful approach to the evaluation of suspected myeloneuropathy requires

- *an understanding of spinal cord*
- *peripheral nervous system anatomy and*
- *physiology,*
- *careful history and neurologic Exam*
- *appropriate utilization and interpretation of diagnostic testing.*

Recognition

Recognition of a myeloneuropathy may be challenging because symptoms can be similar to those of purely spinal cord or peripheral nerve disease,

examination findings may be more prominently myelopathic or (peripheral) neuropathic, making it more difficult to recognize signs of the other.

A diagnostic evaluation

using some combination of

- *Blood work*
- *CSF examination*
- *Radiographic*
- *Electrodiagnostic studies*


A thoughtful, consistent approach to the patient pr
with myeloneuropathy facilitates an accurate diagn
timely treatment and helps to avoid unnecessary t

Conditions known to result in myeloneuropathy

- *metabolic*
- *inflammatory*
- *infectious*
- *toxic*
- *hereditary disorders*

of these disorders is helped by an understanding of the typical mode of onset and progression, the pattern of myelopathic and neuropathic findings,

Recognition

other potential neurologic manifestations

(such as optic neuropathy or cognitive impairment),

Laboratory,

Electrodiagnostic,

Radiographic findings

a slowly progressive spastic paraparesis

associated with a demyelinating PN

in a patient with FH of gait impairment

suggests a hereditary condition such as adrenomyeloneuropathy.

A rapidly progressive sensory ataxia with cervical MRI studies demonstrating T2 hyperintensity in the posterior columns suggests a myeloneuropathy due to either

copper

or

vitamin B12 deficiency.

CLINICAL RECOGNITION OF MYELONEUROPATHY

The initial and most important components of an evaluation leading to a correct diagnosis of myeloneuropathy are a careful history and an examination to localize the disorder within the neuraxis.

Neuropsychiatric disorders

are due to demyelination of cervical, thoracic dorsal, and lateral spinal cords; demyelination of white matter; and demyelination of cranial and peripheral nerves.

Low vitamin B_{12} level

can lead to elevated methylmalonic acid (MMA) and homocysteine levels.

causes abnormality in fatty acid synthesis affecting neuronal membrane.

Elevated homocysteine

is neurotoxic through overstimulation of the N-methyl-D-aspartate (NMDA) receptor and toxic to vasculature through activation of coagulation system and effects on endothelium.

DESCRIPTION

Normal B_{12} absorption

B_{12} present in animal-source foods (meat, fish, eggs, milk) and foods fortified with B_{12}

Dietary vitamin B_{12} (cobalamin) bound to food is cleaved by acids in stomach and bound to haptocorrin (commonly known as R-factor).

Duodenal proteases cleave B_{12} from haptocorrin.

In duodenum, B_{12} uptake depends on binding to intrinsic factor (IF) secreted by gastric parietal cells.

B_{12} -IF complex is absorbed by terminal ileum into portal circulation.

Body's B_{12} stored in liver = 50-90%

- *B_{12} secreted into bile from liver recycled via enterohepatic circulation*
- *Delay 5 to 10 years from onset of B_{12} deficiency to clinical symptoms due to hepatic stores and enterohepatic circulation*

Typical Western diet: 5 to 30 µg/day; however, only 1 to 5 µg/day is effectively absorbed.

- *Recommend 2.4 µg/day for adults and 2.6 µg/day during pregnancy and 2.8 µg/day during lactation (most prenatal vitamins contain B_{12})*

EPIDEMIOLOGY
Prevalence

Endemic area: Northern Europe, including Scandinavia; more common in those of African ancestry

Increasing recognition in breastfed-only infant populations with vitamin B_{12} deficient mothers

EPIDEMIOLOGY
Prevalence

Prevalence 5-20% in developed countries

- *12% in elderly living in community*
- *30-40% in elderly in institutions, sick, or malnourished*
- *5% patients in tertiary reference hospitals*

Prevalence by age group

- *20 to 39 years old: prevalence 3%*
- *40 to 59 years old: prevalence 4%*
- *>70 years old: prevalence 6%*

ETIOLOGY AND PATHOPHYSIOLOGY

Decreased oral intake

Vegetarians and vegans: B_{12} is found in animalsource foods; however, strict vegetarians uncommonly develop deficiency because only 1 mg/day is needed, with adequate amounts present in legumes.

Decreased IF

Pernicious anemia (PA):

can be associated with autoantibodies directed against gastric parietal cells and/or IF

Chronic atrophic gastritis: autoimmune attack on gastric parietal cells causing autoimmune gastritis and leading to decreased IF production

Gastrectomy: Removal of entire or part of stomach decreases amount of parietal cells.

Decreased ileal absorption

Crohn disease: Terminal ileal inflammation decreases body's ability to absorb B_{12}.

Chronic alcoholism: decreases body's ability to absorb B_{12}

Ileal resection

Pancreatic insufficiency: Pancreatic proteases are required to cleave the vitamin B_{12}-haptocorrin bond to allow vitamin B_{12} to bind to intrinsic factor.

Helicobacter pylori infection impairs release of B_{12} from bound proteins.

Medications:

Proton pump inhibitors (PPIs)

H_2 antagonists

Antacids decrease gastric acidity, inhibiting B_{12} release from dietary protein; metformin

Hereditary (rare)

Imerslund-Grasbeck disease (juvenile megaloblastic anemia)

Congenital deficiency of transcobalamin

Severe methylene tetrahydrofolate reductase deficiency

Abnormalities of methionine synthesis

Causes Food-cobalamin malabsorption syndrome

As many as 60-70% of cases

Primary cause in elderly

Pathophysiology: inability to release cobalamin from food or binding protein, especially if in the setting of hypochlorhydria

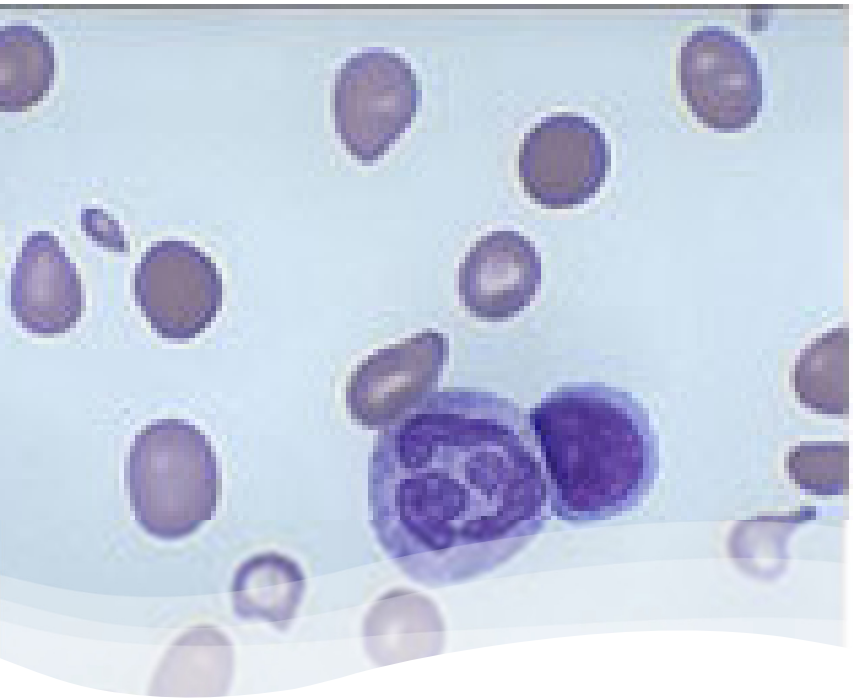
Seen in atrophic gastritis, long-term ingestion of antacids and biguanides, possible relationship to H. pylori infection

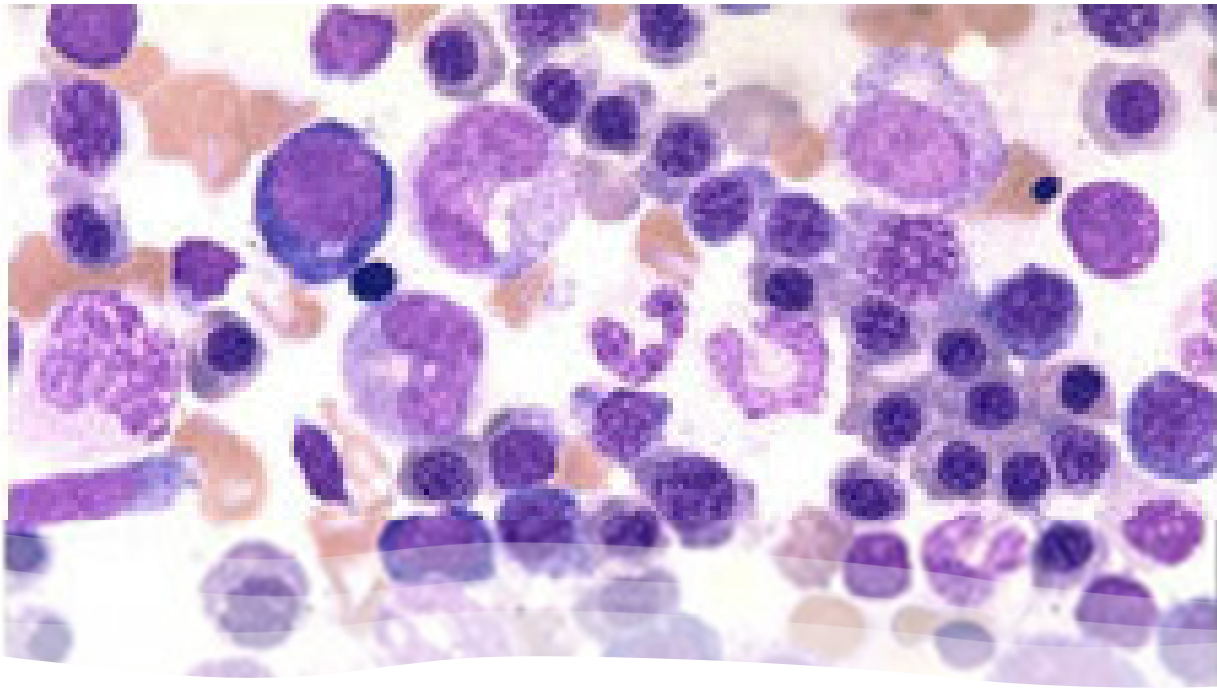
Pernicious anemia

15-30% of all cases; most frequent cause of severe disease.

Neurologic disorders are common presenting complaints.

Common in elderly, as high as 20%, with mild atrophic gastritis, hypochlorhydria, and impaired release of dietary vitamin B_{12}





Pernicious anemia

Pernicious anemia

Autoimmune disease with destruction of gastric fundal mucosa cells via a cell-mediated process

Anti-gastric parietal cell antibodies: sensitivity >90%, specificity 50%; use for screening test

Anti-intrinsic factor antibodies: sensitivity 50%

Associated with other autoimmune diseases

Insufficient dietary intake: 2% of cases; vegans or long-standing vegetarians

Infants born to vitamin B_{12}-deficient mothers may have deficiency or develop it if breastfed exclusively.

Intestinal causes:

1% of cases; prevalence depends on risk factors, such as surgical conditions

Gastrectomy: due to decreased production of intrinsic factor

Gastric bypass: appears 1 to 9 years after surgery, prevalence 12-33%

Ileal resection or disease

Fish tapeworm

Severe pancreatic insufficiency

1/10 of cases

Genetics

Imerslund-Grasbeck disease (juvenile megaloblastic anemia) caused by mutations in the amnionless (AMN) or cubilin (CUBN) genes with autosomal recessive pattern of inheritance; inadequate ileal uptake of B_{12}-IF complex and B_{12} renal protein reabsorption

GENERAL PREVENTION

Risk factors: vegan diet, age >65 years, female, chronic atrophic gastritis, Crohn disease or other ileal disorders, chronic medication use including PPI, metformin, H_2 antagonists

DIAGNOSIS

Symptoms and physical exam findings:

- *Asymptomatic patients*
- *Hematologic*
- *Neuropsychiatric*
- *Digestive*
- *Other*

DIAGNOSIS

Symptoms and physical exam findings:

Asymptomatic patients *may be diagnosed by the incidental finding of anemia or an elevated mean corpuscular volume (MCV) during routine testing or evaluation of unassociated disorders.*

DIAGNOSIS
Hematologic

Frequent: *macrocytosis, neutrophil hypersegmentation, spinal cord medullar megaloblastosis (blue spinal cord)*

Rare: *isolated thrombocytopenia and neutropenia, pancytopenia*

Very rare: *hemolytic anemia, thrombotic microangiopathy with schistocytes*

Neuropsychiatric DIAGNOSIS

Frequent:

Classic, but uncommon:

Neuropsychiatric DIAGNOSIS

Frequent:

- *Sensory polyneuritis*
- *Paresthesias*
- *Babinski sign*
- *Weakness*
- *Gait unsteadiness*
- *Loss of proprioception*

(impaired vibratory sensation, positive Romberg, ataxia, hyperreflexia)

Neuropsychiatric DIAGNOSIS

Classic, but uncommon:
subacute combined degeneration of spinal cord associated with PA

Myelin degeneration in the lateral and posterior columns;

- *Ataxia*
- *Proprioception and vibration loss*
- *Bowel and bladder incontinence*
- *Orthostatic hypotension*
- *Decreased memory*
- *Mania*
- *Delirium*
- *Psychosis*
- *Depression*

Digestive DIAGNOSIS

Classic: Hunter glossitis, jaundice, and high lactate dehydrogenase and bilirubin

Possible: abdominal pain, dyspepsia, nausea, vomiting, diarrhea

Rare: mucocutaneous ulcers

Other DIAGNOSIS

Frequent: *pallor, edema, jaundice*

Under investigation: *chronic vaginal and urinary infections, atrophy of vaginal mucosa, hypofertility, venous thromboembolism, angina, miscarriages*

Commonly insidious and nonspecific; *thus, delay in diagnosis is common.*

HISTORY

Underlying disease associated with vitamin B_{12} deficiency
Fatigue, anorexia
Depression
Falls (due to diminished proprioception)
Loss of sensation in "stocking-glove" distribution
Glossitis/loss of sense of taste, and other subtle, nonspecific neurologic symptoms

DIAGNOSTIC TESTS & INTERPRETATION

Measurement of vitamin B_{12}, CBC (MCV)

DIAGNOSTIC TESTS & INTERPRETATION

Measurement of B_{12} may be low or low normal depending on institution's cutoff value.

65-95% sensitivity levels <200 pg/mL

MMA and homocysteine

May need additional tests such as MMA and homocysteine if vitamin B_{12} level is low normal (<350 pg/mL) and no evidence of anemia depending on clinical suspicion

Measurement of MMA

If high suspicion on normal B_{12} with high/normal MCV, consider testing MMA and homocysteine levels.

MCV often increased

Measurement of MMA

- *More sensitive and specific than homocysteine*
- *Levels increased in renal failure and volume depletion*

Measurement of homocysteine

Levels increased in folate deficiency, renal failure, and homocystinuria

MMA and homocysteine levels only reliable in an untreated patient, as levels fall with supplementation

DIAGNOSTIC TESTS & INTERPRETATION

Other tests: folate and other markers of anemia (iron studies)

MCV may be normal, decreased, or increased if vitamin B_{12} deficiency coexists with other forms of anemia, such as iron deficiency or hemolysis.

Thus, RBCs may be normochromic, normocytic, or hypochromic microcytic.

ALERT

Low levels of vitamin B_{12} are seen in folate deficiency, HIV, and multiple myeloma.

Elevated levels of vitamin B_{12} are seen in renal disease, occult malignancy, and alcoholic liver disease and as a result of technical error.

ALERT

Macrocytosis may be due to

- *Folate deficiency*
- *Reticulocytosis*
- *Medications*
- *Bone marrow dysplasia*
- *Hypothyroidism*

or be masked by concomitant microcytic anemia.

ALERT

Serum homocysteine and MMA

Elevated in B_{12} deficiency secondary to decreased metabolism

If both are normal, B_{12} deficiency is effectively ruled out.

If MMA is normal and homocysteine is increased, think folate deficiency.

ALERT

For pernicious anemia

Check antibody to intrinsic factor;

Positive test is confirmatory for PA*, but sensitivity is only 50-70%.*

Anti-parietal cell antibody positivity *indicates PA.*

For patients who are antibody positive, consider screening for autoimmune thyroid disease.

Pregnancy Considerations

Because ***B_{12} crosses the placenta****, pregnant women with low levels of B_{12} are at higher risk of having children with neural tube defects, congenital heart defects,* ***developmental delay, and failure to thrive.***

Pregnancy Considerations

Exclusively breastfed infants of mothers who are B_{12} deficient are at risk of developing B_{12} deficiency.

Infants breastfed from B_{12}-deficient mothers might not show signs or symptoms until 4 to 6 months of age, which may include developmental regression, feeding difficulties, lethargy, or hypotonia.

Diagnostic Procedures/Other

Bone marrow exam is usually unnecessary *in the evaluation of* B_{12} *deficiency because of the inability to differentiate from folate deficiency.*

Spinal cord imaging is not standard; *MRI in selected cases, especially with severe myelopathy*

TREATMENT

MEDICATION

Parenteral cyanocobalamin replacement recommended *in patients with severe neurologic symptoms:*

IM cyanocobalamin:

- *1,000 µg/day for 7 days, then*
- *1,000 µg weekly for 4 weeks, then*
- *1,000 µg monthly for life*

High-dose, daily oral cyanocobalamin at doses of 1,000 to 2,000 µg *are as effective as monthly intramuscular injection and is the preferred route of initial therapy in most circumstances because it is cost-effective and convenient.*

Requires greater patient compliance.

Transnasal and buccal preparations of cyanocobalamin *are also available; however, further study is needed.*

ALERT

Folic acid without vitamin B_{12} in patients with PA is contraindicated; it will not correct neurologic abnormalities.

Hematologic Monitoring

Reticulocytosis in 1 week

Rise in hemoglobin beginning at 10 days; usually will return to normal in 6 to 8 weeks

Monitor potassium in profoundly anemic patients (hypokalemia due to potassium use).

Serum MMA decreases with replacement therapy.

Neurologic:

can note improvement within 3 months of treatment; however, maximum improvement noticed at 6 to 12 months.

Some symptoms may be irreversible.

DIET

Meat, animal protein, and legumes unless contraindicated

Clinical Pearls

Consider screening for B_{12} deficiency in high-risk patients including the elderly and monitoring B_{12} levels annually if on metformin or ***on chronic PPIs.***