Neglected Clinic Topics

Things your PD provider(s) should be talking to you about, but probably aren’t…
Disclosures

Ongoing Relationships:

- **Teaching:** Online Parkinson’s School
- **Clinic:** Seattle Integrative Medicine
- **Research:**
  - University of Washington/ MJ Fox Foundation-ATP in PD Muscle
  - Bastyr University/ Community donations- CAM Care PD
- **Industry**
  - ParK-9- PD Screening test (Dogs smell ear wax and say yes/no)
- The Brain Collaborative —- *stay tuned*…
We are Clueless

None of us know:

• What PD is
• What caused it
• What your future looks like
• How to slow/ stop progression
• How to encourage recovery/ neuroplasticity
Many Things Cause Parkinsonism

- Heavy metals, e.g. manganese
- B-12 deficiency
- Celiac disease
- Autoimmune disease
- Vascular parkinsonism
- Genetic parkinsonism
- Infection, e.g. H. Pylori infection
- Pesticides
- Ochratoxin A?

If your parkinsonism isn’t caused by one of these other things,
- starts on 1 side
- responds well to levodopa
—> then we call it idiopathic PD
B-12 deficiency-induced parkinsonism

Involuntary movements due to vitamin B12 deficiency.

De Souza A, Moloi MW.

Abstract

Deficiency of vitamin B12 produces protean effects on the nervous system, most commonly neuropathy, myelopathy, cognitive and behavioural symptoms, and optic atrophy. Involuntary movements comprise a relatively rare manifestation of this readily treatable disorder. Both adults and infants deficient in vitamin B12 may present with chorea, tremor, myoclonus, Parkinsonism, dystonia, or a combination of these, which may precede diagnosis or become apparent only a few days after parenteral replacement therapy has begun. The pathogenesis of these movement disorders shows interesting parallels to certain neurodegenerative conditions. The clinical syndrome responds well to vitamin B12 supplementation in most cases, and an early diagnosis is essential to reverse the haematological and neurological dysfunction characteristic of this disorder. In this article, we elucidate the association of vitamin B12 deficiency with movement disorders in adults and in infants, discuss the pathogenesis of this association, review previously reported cases, and present a young adult male with severe generalized chorea that showed a salutary response to vitamin B12 supplementation.

 Stops progressing once B12 is adequately supplemented
Not everyone needs to take B12
Everyone with parkinsonism should be tested for B12 deficiency
(Methylmalonic acid, homocysteine, B12)
H. Pylori in PD

• ...

LK Mischley Feb 2021
PD Community & PD Personality

- The best part of Parkinsonism is the PD community
  - Like it or not, you’re in a club [of pretty awesome people]
- There IS a PD personality and PwP are a pleasure to be around

A TRIBE

- APDA Support Groups
- World Parkinson’s Congress
- PD Summer School
- PD Yoga, PWR!, RSB, singing, tango, pickle ball, table tennis…

LK Mischley Feb 2021
You’ve Had This a Long Time

Parkinson’s disease and dementia with Lewy bodies: a prospective study
Nonmotor Symptoms
Non-Motor Symptoms Can Be As/More Debilitating than Motor Symptoms

- On the PRO-PD, 2/3 of symptoms are attributable to non-motor symptoms

- Why?
  - We have excellent treatment options for motor symptoms
  - We have very few treatment options for nonmotor symptoms

N > 2000 PwP
CAM Care PD dataset 2020

LK Mischley Feb 2021
# Symptoms According to Patients

<table>
<thead>
<tr>
<th>Percent of Patients Reporting Symptom</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-85%</td>
<td>Fatigue, Impaired Handwriting, Hyposmia</td>
</tr>
<tr>
<td>70-80%</td>
<td>Memory impairment, Muscle pain, Daytime sleepiness, Slowness, Tremor, Sexual impairment, Balance, Urinary dysfunction, Stooped posture</td>
</tr>
<tr>
<td>60-70%</td>
<td>Lack of motivation, Insomnia, Difficulty walking, Anxiety, Difficulty rising, Impaired speech</td>
</tr>
<tr>
<td>50-60%</td>
<td>Constipation, Difficulty dressing, Depression, Withdrawn, Acting out dreams, Comprehension, Restless legs, Drooling</td>
</tr>
<tr>
<td>40-50%</td>
<td>Dizzy on standing, Visual disturbance, Falls</td>
</tr>
<tr>
<td>30-40%</td>
<td>Dyskinesia, Freezing</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>Nausea, Hallucinations</td>
</tr>
</tbody>
</table>
Stress Exacerbates PD Symptoms

- Distress- bad stress; e.g. illness, injury, loss
- Eustress- good stress; e.g. exercise, travel, planning a wedding
- Emotional stress- death of a loved one, social isolation
- Physical stress- injury, infection
Why Me?
Risk Factors for PD Diagnosis

**INCREASE RISK**

- Pesticides
- Dairy
- Melanoma
- TBI

*Figure 4: The balance of genetic and environmental factors that underlie Parkinson's disease occurrence*

Larger weights have been used for those factors with stronger epidemiological evidence. We have included only factors supported by multiple prospective studies, but the presentation is not exhaustive and it is meant only for illustrative purposes. Factors included might or might not be causal. TBI=traumatic brain injury. PD=Parkinson’s disease. CCBs=calcium channel blockers.

LK Mischley Feb 2021

Risk Factors for PD Diagnosis

DECREASE RISK

- Smoking
- Caffeine
- Urate
- Exercise
- Ibuprofen
- Ca-channel blockers

Figure 4: The balance of genetic and environmental factors that underlie Parkinson’s disease occurrence
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Exercise
Poll

At almost every visit, my PD provider reminds me about the important role of exercise for managing PD:

A) True

B) False
Exercise & Social Health Are Associated with Improve Outcomes Over Time

Subramanian I, et al, 2020

Less Severe Patient-Reported PD Symptoms

More Severe Patient-Reported PD Symptoms
Synergy of pandemics-social isolation is associated with worsened Parkinson severity and quality of life

Indu Subramanian, Joshua Farahnik and Laurie K. Mischley

**Fig. 5** Individual symptom severity in lonely versus not-lonely individuals with PD. Lonely individuals rated all symptoms as more severe than their non-lonely counterparts. Among lonely individuals, the greatest discrepancy between the two cohorts was for "withdrawal/loss of interest," "motivation/initiative," "depression," and "anxiety."
Medications
We are working for you. You are calling the shots.

Patients are paying providers to provide advice, counsel, and direction as they navigate PD. Patient-centered approach.

Before any medication is prescribed, the physician should discuss with you the likely benefits/risks, so that you can make an informed decision.

There is no rush to start meds… you’ve likely had this disease for a decade or two+, you can take a few months to get oriented and educated.

Your quality of life is likely to improve when you do start medication…. Don’t dilly-dally.
Levodopa- Protein

- Is an amino acid and works by filling amino acid receptors. If you have any amino acids your stomach when you take your medication (protein), it will reduce the amount of L-dopa you absorb. Protein hides everywhere and doesn’t move through you as fast as most people think it does.

- Level 1- Avoid dietary protein 1 hr before or 2 hr after meds

- Level 2 - Protein Redistribution Diet (save protein for the evening meal)
Levodopa Interferes with B-vitamins

- MTHFR polymorphism
- Elderly
- Alcohol
- Levodopa use
- Malnutrition
- Folic acid deficiency
- B12 deficiency
- B 6 deficiency
- Betaine deficiency

Elevated Homocystine

- Enhanced rate of Parkinson's disease progression
- Cognitive Decline
- APOE-4 allele

Enhanced rate of Parkinson's disease progression

APOE-4 allele
Levodopa Interferes with B-vitamins

- This does NOT mean you shouldn’t take levodopa.
- This does mean that the physician that prescribes your levodopa should measure your homocysteine annually and prescribe a homocysteine-lowering B-vitamin supplement if your levels rise > 10.
Homocysteine in PD

• High homocysteine at baseline predicts greater cognitive decline over time.
  Mov Disord 2018; 33(5):762-770

• Elevated “homocysteine is significantly associated with some aspects of cognitive function in PD, and may represent a treatable risk factor for cognitive decline in PD.”
  Parkinsonism Relat Disord 2019; 44:1-5.
Dopamine Agonists

**PROS**

- Smoother, more long-acting than levodopa
- Very effective at treating restless leg syndrome

**CONS**

- Less effective than levodopa
- While on the medication, many people experience
  - **Daytime sleepiness** (nodding off while eating, reading, driving)
  - **Impulse control disorders** (shopping, punding, gambling, sex)
- When you eventually come off the medication, ~19% of people experience DAWs (PMID: 28104232)
- **Dopamine Agonist Withdrawal Syndrome**
Laboratory Testing
Biomarkers in PD

- Just because there is not a single biomarker that serves as an accurate surrogate for PD severity and progression,
- Doesn’t mean that there aren’t dozens of biomarkers that do predict better/worse outcomes
- Very few neurologists routinely measure labs
  - **How does one make decisions without data?**
Vitamin D in PD

Systematic Review of the Relationship between Vitamin D and Parkinson’s Disease

Table 2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PD</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato 1997 H&amp;Y 3–5</td>
<td>Mean 8.9</td>
<td>Mean 21.6</td>
<td>SD 3.2</td>
<td>SD 3.1</td>
</tr>
<tr>
<td>Sato 2005</td>
<td>Mean 11.9</td>
<td>Mean 33.3</td>
<td>SD 6.5</td>
<td>SD 3.1</td>
</tr>
<tr>
<td>Abou-Rayya 2009</td>
<td>Mean 12.9</td>
<td>Mean 21.6</td>
<td>SD 9.9</td>
<td>SD 4.8</td>
</tr>
<tr>
<td>Evan 2011</td>
<td>Mean 31.9</td>
<td>Mean 37</td>
<td>SD 13.6</td>
<td>SD 14.5</td>
</tr>
<tr>
<td>Vandens Bos 2013</td>
<td>Mean 19.3</td>
<td>Mean 22.7</td>
<td>SD 8.1</td>
<td>SD 9.2</td>
</tr>
<tr>
<td>Peterson 2014</td>
<td>Mean 15.7</td>
<td>Mean 16.4</td>
<td>SD 9.6</td>
<td>SD 9.9</td>
</tr>
<tr>
<td>Total</td>
<td>Mean 20.3</td>
<td>Mean 21.4</td>
<td>SD 10.0</td>
<td>SD 10.0</td>
</tr>
</tbody>
</table>

Heteregeneity: Chi² = 474.94, df = 5 (P < 0.00001); P = 99%
Test for overall effect: Z = 33.99 (P < 0.00001)

H&Y = Hoehn and Yahr.
Vitamin D in PD

- In PD, low vitamin D has been linked to:
  - Slower bowel transit time (constipation)
  - Elevated hsCRP (inflammation)
  - Impaired balance, muscle weakness
  - Depression
  - Risk of dementia

- Target: 60-80 ng/ml

- Dose depends on
  - Obesity, Time outdoors, skin coverage, ...
  - In Seattle, if <30 ng/ml, Rx: 10,000 IU/d vit D 3 for 3 months, then retest.

- Toxicity occurs ~ 300 ng/ml (Jones 2008)
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Deficiency of vitamin B12 produces protean effects on the nervous system, most commonly neuropathy, myelopathy, cognitive and behavioural symptoms, and optic atrophy. Involuntary movements comprise a relatively rare manifestation of this readily treatable disorder. Both adults and infants deficient in vitamin B12 may present with chorea, tremor, myoclonus, Parkinsonism, dystonia, or a combination of these, which may precede diagnosis or become apparent only a few days after parenteral replacement therapy has begun. The pathogenesis of these movement disorders shows interesting parallels to certain neurodegenerative conditions. The clinical syndrome responds well to vitamin B12 supplementation in most cases, and an early diagnosis is essential to reverse the haematological and neurological dysfunction characteristic of this disorder. In this article, we elucidate the association of vitamin B12 deficiency with movement disorders in adults and in infants, discuss the pathogenesis of this association, review previously reported cases, and present a young adult male with severe generalized chorea that showed a salutary response to vitamin B12 supplementation.
Among people with Parkinson’s disease, people with a value greater than 0.8 mg/L at baseline were less likely to be alive 10 years later.
hsCRP in PD

Conclusions:

• hsCRP levels were significantly higher in newly diagnosed PwP than is seen in healthy controls.

  (IU Song, et al. 2011. Assoc between hsCRP and risk of early iPD.)

• “CONCLUSION: We suggest that our results could support the hypothesis that neuroinflammation contributed to the pathogenesis of PD and cautiously assume that elevated hs-CRP might have a clinical value as a risk factor for PD.”

Conclusions

Baseline CRP concentrations were associated with the risk of death and predicted life prognosis of patients with PD. The associations were independent from PD duration, PD severity, cognitive function, ages, and nutritional conditions, suggesting the possibility that subclinical chronic inflammation is associated with a neurodegenerative process in PD.

PMID: 26218286
Can hsCRP Be Lowered?

- Yellow, red, & orange fresh fruits & vegetables (carotenoids)
- Citrus, greens, berries (vit C)
- Soy (tofu, tempeh, miso)
- Non-fried fish

“High intakes of **carotenoids** and **vitamin C**, but not of vitamin E, seem to decrease the level of circulating hs-CRP. In addition, high consumption of vegetables and fruits are associated with lower levels of circulating hs-CRP, perhaps by exerting anti-inflammatory effects.”


“In a Japanese population, high intakes of **vegetables, fruit, soy products, and fish** was significantly and inversely related to hs-CRP concentrations.”

Diet
• There is no double-blind, placebo-controlled trial that says changing your diet will change your outcomes (yet)

• The Mediterranean diet and the MIND diet have been shown to be associated with decrease risk of PD diagnosis and delay in diagnosis.

• The CAM Care PD study shows people that acquire more symptoms faster are eating very differently than patients that are not progressing or having a very slowly progressing disease. (Mischley LK, et al 2017)
Diet Behaviors

Impact of Dietary Behaviors on PD Progression

- I cook most of my meals
- I avoid artificial sweeteners
- I avoid artificial colors, flavors
- I routinely prepare meals for others
- I try to eat organically grown foods when possible
- I buy from local farmers
- I find it difficult to afford healthy food
- It is difficult to afford groceries

N = 1503-1521 (per question, if answered).
All regression analyses adjusted for age, gender, income, and years since diagnosis.
Impact of 2-4 Servings Per Week on Symptom Severity

Food Choices & Parkinson's Disease Progression

For study details:
www.LivingHeathyWithParkinsons.com

To participate in this study:
www.CAMCarePD.Bastyr.edu
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Our research might be wrong. It might be that people that are doing really well crave more broccoli and it’s not the broccoli that helps…

Your physician’s job is to make you aware of your therapeutic options

- S/he should give your their opinion about why you should/ should not encourage plants and avoid soda.
  - e.g. “Until there’s a double-blind placebo-controlled trial…”

They should be telling you that these data exist and discussing the strengths/ limitations of these data with you.
Summary
Your health care team is working for you. YOU are the boss. We are your employee.

Do not be shy about asking questions, trying to understand your choices, asking for referrals, etc.

Bring a list of questions to your provider, so you can make sure that the things on your list don’t get neglected. (Med management is often prioritized over sleep, ED, fatigue, loneliness, etc.)

Understand that your physician can’t keep up with all the literature coming out. S/he may be VERY up-to-date on DBS, but not on diet and exercise— that’s OK!

It’s OK to have a team of providers with different expertise.
Thank You

AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.