



PHARM NOTES



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Pick's Disease

Pick's disease is a rare degenerative brain disease, accounting for 0.4 to 2% of all dementias, that was described originally in 1892 by Arnold Pick. Pick had noticed a gradual mental deterioration over a period of years in one of his patients. On autopsy he discovered severe frontal and temporal brain atrophy and a spongy appearance to the neuronal tissue. In later years, with the advent of the microscope, it was discovered that this tissue contained an abnormally excessive amount of a ubiquitous native neuronal protein known as tau.

Although originally confused with Alzheimer's disease, Pick's disease is now recognized as a subtype of a larger group of neurological disorders called frontotemporal dementias. Frontotemporal dementias are categorized by atrophy of the frontal and temporal lobes. In 60% of the cases the atrophy is asymmetric, affecting mainly the left hemisphere. Other subtypes of frontotemporal dementias include progressive aphasia and semantic dementia. Clinically, any frontotemporal dementia presents with classic symptoms of personality changes and/or language problems. However, Pick's disease has a characteristic pathology, containing tau proteins that are clumped into "pick bodies".

Behavioral change is the most common presentation and will affect up to 90% of Pick's disease patients. This characteristic often helps to clinically distinguish Pick's disease from other dementias. Personality changes can include apathy; inappropriate social behavior; lack of social tact; lack of empathy; distractibility; loss of insight into the behaviors of oneself and others; an increased interest in sex; changes in food preferences; agitation or, conversely, blunted emotions; neglect of personal hygiene; repetitive or compulsive behavior, and decreased

energy and motivation. The key component of these changes is that the behavior is aberrant from a baseline behavior and that it continues for an extended period of time.

Often accompanying these behavior disturbances are language dysfunctions, including difficulty making or understanding speech. Language dysfunction is usually the presenting symptom of Pick's disease. However, these changes can be difficult to identify in the early stages of the disease. As the language disorder progresses, abnormalities such as logorrhea (abundant unfocused speech), echolalia (spontaneous repetition of words or phrases), and palilalia (compulsive repetition of phrases) may occur. Motor deficits, while rarer, may present in some Pick's disease patients. These symptoms are usually extrapyramidal in nature. Cognitive deficits are often minimal.

Pick's disease normally occurs between the ages of 35 and 75 years, and only rarely after age 75. This is in contrast to Alzheimer's Disease, for which the incidence increases rapidly after age 75. Pick's disease is also a more rapidly progressive disorder than Alzheimer's disease with a symptom onset of 8.7 versus 11.8 years. The disease may last from 3 to 17 years before death, with an average duration of eight years after diagnosis.



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In-service: G6PDD Deficiency

Definition

Glucose-6-phosphate dehydrogenase deficiency (G6PDD) is an X-linked, recessive hereditary genetic defect caused by mutations in the *G6PD* gene, resulting in protein variants with different levels of enzyme activity, that are associated with a wide range of biochemical and clinical phenotypes. It is recognized that the G6PD enzyme plays an important role in red blood cell function and subsequently that individuals with the disease may exhibit inherited hemolytic anemia in response to a myriad of causes. The term favism is often interchanged with G6PDD, as many patients with the disease also confer a fava bean allergy.

Epidemiology

G6PDD is estimated to affect more than 400 million people globally, most prevalently in Africa, making it the most common human enzyme defect. The G6PDD worldwide distribution pattern strongly resembles that of malaria; happenstance serves that a side effect of the disease is conferred protection against malaria, perhaps giving carriers an evolutionary advantage.

Clinical Presentation

Most G6PDD individuals, usually male due to an X-linked inheritance, are asymptomatic throughout their life. For those less fortunate, the deficiency usually presents as neonatal jaundice or an acute hemolytic anemia, arising when red blood cells undergo oxidative stress, in response to certain drugs, foods, or illness. Thus G6PDD can present as drug-induced [see **Causative agents**], infection-induced (paradigms include Hepatitis A and B and pneumonia), or favism (food-induced). Regardless of the hemolytic cause, G6PDD is characterized clinically by fatigue, back pain, anemia, and jaundice. Clinical disease markers are increased unconjugated bilirubin, lactate dehydrogenase, and reticulocytosis. A decrease in the hemoglobin level is the most readily ascertained sign of drug-induced G6PDD-related hemolysis.

Causative Agents

There are many drugs that have been linked to acute hemolysis in G6PDD individuals:

	Definite association	Possible association	Doubtful association
Antimalarials	Primaquine Pamaquine	Chloroquine	Mepacrine Quinine
Sulfonamides	Sulfanilamide Sulfacetamide Sulfapyridine Sulfamethoxazole	Sulfadimidine Sulfasalazine Glibenclamide	Aldesulfone Sulfadiazine Sulfafurazole
Sulfones	Dapsone
Nitrofurantoin	Nitrofurantoin
Antipyretic or analgesic	Acetanilide	Aspirin	Paracetamol Phenacetin
Other drugs	Nalidixic acid Niridazole Methylthionium Phenazopyridine Co-trimoxazole	Ciprofloxacin Chloramphenicol Vitamin K analogues Ascorbic acid Mesalazine	Aminosalicic acid Doxorubicin Probenecid Dimercaprol
Other chemicals	Naphthalene 2,4,6-trinitrotoluene	Acalypha indica extract	

Reprinted from ref 1 with permission.

Table 2: Drugs and chemicals associated with substantial haemolysis in patients with G6PD deficiency¹



In-service: G6PDD Deficiency

Drug-induced G6PDD has several causative agents typically consisting of antimalarials, sulfonamides, nitrofurantoin, and antipyretic (anti-fever) drugs, among others including Co-trimoxazole and possibly ciprofloxacin. Avoiding these drugs is imperative in deficient individuals [see **Management**].

Diagnosis

The NADPH fluorescence test is a qualitative test and is the gold standard for G6PDD screening, taking only 15 minutes to perform and requiring merely a blood spot on filter paper. Laboratory analysis will include a CBC and reticulocyte count, and liver enzymes, haptoglobin, Coombs' test, and TSH to rule out other causes.

G6PDD Classification

- I. **Severely deficient, associated with chronic non-spherocytic hemolytic anemia.**
- II. **Severely deficient (1-10% residual activity), associated with acute hemolytic anemia.**
- III. **Moderately deficient (10-60% residual activity).**
- IV. **Normal activity (60-150%).**
- V. **Increased activity (> 150%).**

Management

Prevention is the most effective management strategy concerning G6PDD. In order to prevent hemolysis, the breaking of red blood cells, it is necessary to avoid oxidative stressors (e.g. causative drugs and fava beans). However, for this management strategy to be effective, awareness of G6PDD is necessary either as a result of a past episode or having undergone a screening program; as previously mentioned, most individuals remain asymptomatic through their life.

Neonatal jaundice is treated using phototherapy. General treatment strategies, varying with each individual, include antioxidants, iron-chelation, and in cases of hemolytic crisis, blood transfusions. Antioxidants, such as vitamin E, lack data supporting their use. Blood transfusions offer the symptomatic benefit of red blood cells that are not G6PD deficient. G6PDD individuals should be given folic acid to help promote normal red blood cell production. Aside from drug and food-induced G6PDD, staying current with vaccinations may help to prevent infection-induced G6PDD, namely that caused by hepatitis.

*Article by Matthew Hogan, UNC Chapel Hill
Pharm.D. Candidate*



New Drug Update: Amitiza®

Brand Name: Amitiza

Generic Name: lubiprostone

Pharmacologic category: chloride channel activator, gastrointestinal agent

Use: Treatment of chronic idiopathic constipation

Chronic idiopathic constipation – constipation of an unknown origin, may be caused by hormonal changes, neural disorder or muscle malfunction in the intestine, rectum, or anus.

Mechanism of Action: bicyclic fatty acid that acts at the apical portion of the intestine as a chloride channel activator stimulating intestinal water secretion and motility.

Dosage: 24 mcg twice daily, may reduce dose to 24 mcg once daily in cases of severe nausea

Administration: with food to minimize nausea

Adverse effects: Nausea 29%, Headache 11%, Diarrhea 12% (adverse effects reported > 10%), various other reported < 10%

Contraindications: Allergies to any component of lubiprostone.

Pregnancy: (C) Studies with animals Amitiza did produce fetal loss. Amitiza should not be used in women of child bearing age without a pregnancy test first.

Warnings/Precautions: Avoid use in patients with diarrhea or GI mechanical obstruction. No data is available for patients with hepatic or renal impairment. Use with caution in patients concomitantly taking SSRIs, lithium, valproic acid, and carbamazepine (N/V are common and these medications may produce additive effects).

Overdosage/Toxicology: Symptoms of overdose may include nausea, vomiting, diarrhea, dizziness, loose/watery stools, headache, flushing, dyspnea, abdominal pain/discomfort, syncope, xerostomia, and chest discomfort. Supportive treatment required.

Storage: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Cost: Amitiza 24 mcg (30 capsules) ~ \$100

Evidence: There is no long term study data for Amitiza.

There is limited data in elderly populations(>65), and no data for pediatric populations (<18).

A double blinded dosage study was performed with Amitiza in three different groups. Group 1 received 24 mcg daily, group 2 received 24 mcg twice daily, and group 3 received 24 mcg three times daily. Groups 2 and 3 produced the most efficacious but no statistical difference was seen between these 2 groups.

http://www.sucampo.com/downloads/2006.02.01_AMITIZA.pdf

Several studies exist that prove Amitiza is superior to placebo in the treatment of chronic constipation. Amitiza provided > 3 spontaneous bowel movements per week on a weekly basis in treatment groups on average about 20% more of the time than placebo (72% vs. 50%).

http://www.fda.gov/cder/foi/nda/2006/021908s000_Etreva_STATR.pdf

A randomized, double-blinded, placebo controlled trial comparing miralax to placebo was conducted performed to see if miralax was superior to placebo in the treatment of chronic constipation. Results of the study showed that 17 grams of miralax once daily dosing was superior to placebo. Patients received relief from constipation 52% of the time vs. 11% of the time for placebo (p < 0.001). (DiPalma, J.A. Am J Gastroenterol 2007;102:1436–1444)

Recommendation: Amitiza has proven efficacy in the treatment of chronic idiopathic constipation. However there are numerous other medications with better side effect profiles that are available at a lower cost. Amitiza should be reserved for patients that fail therapy with other treatment regimens first.

*Article by Nathan Payne, PharmD. Candidate
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Compression Stockings & Deep Vein Thrombosis

Compression Stockings:

Compression stockings are used to help support the venous and lymphatic systems of the legs. The stockings provide maximum pressure around the ankle and decrease as they move up the leg. The compression is designed to help along with the muscle pump of the calf to keep blood flow from remaining stagnant in the lower extremities. When blood flow slows the chance for clot formation increases.

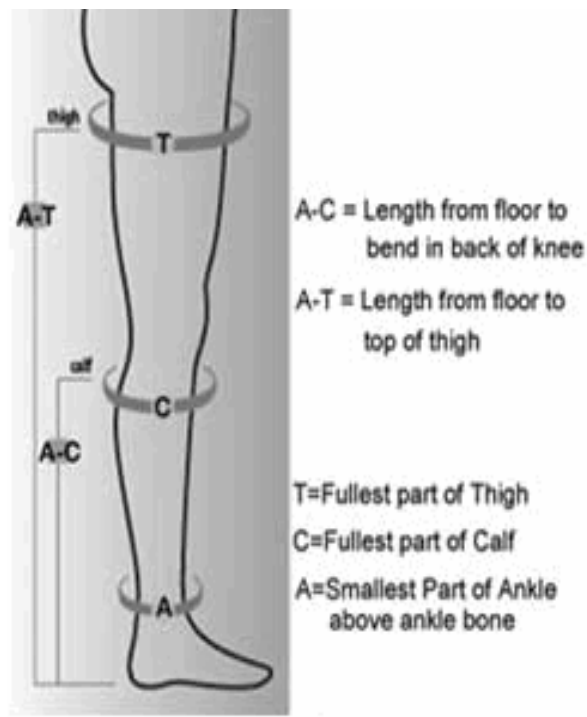
There is limited data on the use of compression stockings for patients that have suffered from a DVT. The American College of Chest Physicians do however recommend that patients that have suffered from a DVT use a compression stocking with a pressure between 30-40 mm Hg for a period of 2 years post DVT. This comes from data obtained in three separate trials that showed a statistically significant difference decrease in post-thrombotic syndrome recurrence in those that used compression stockings versus those that did not. The stockings used in these trials were all below the knee type.

Stockings should be worn from the time a patient awakes until bedtime.

Knee high vs. Thigh high stockings: There is evidence that thigh length stockings provide better prophylaxis for post-thrombotic syndrome in patients that have suffered from a deep vein thrombosis. However, it appears that compliance with thigh length stockings is an issue due to comfort. Patients are more compliant with the knee length stockings due to comfort and ease of use. As with drug therapy compliance is always an issue and if a drug regimen is established that makes a patient more compliant then a better benefit is usually achieved. The same is most likely true with compression stockings.

The average cost of compression stockings is ~ 25 dollars. They can cost as high as 100 dollars. Hand washing and flat drying will maintain the stockings for the longest period of time.

Fitting: most compression stockings come in a box with sizing charts on the back. Below is a diagram of the anatomy to be measured and steps in the measuring process.



Article written by Nathan Payne Pharm. D. Candidate from Wingate University



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Additionally, patients with Pick's disease often suffer from minimum cognitive deficits compared to Alzheimer's disease patients.

Pick's disease is associated with a variety of mutations in the tau gene and is believed to be inherited in up to 40% of cases. Most genetically inherited cases follow an autosomal dominant inheritance pattern. Thus, 50% of the children of an affected individual are at risk for developing Pick's disease. Recently, an association between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia has been discovered. ALS and frontotemporal dementia may overlap. When both occur in families, affected members may have only ALS, only frontotemporal dementia or both. This suggests a relationship in the pathogenesis of these disorders but this relationship is poorly understood and is currently under investigation. Additionally, patients with frontotemporal dementia may go on to develop Parkinson's disease, although these two are not thought to be related. This complexity can make accurate diagnosis of Pick's disease complicated.

In fact, definitive diagnosis can only be made with invasive neurological biopsy. However, an MRI evaluation showing signs of frontotemporal atrophy may yield clues to the presence of Pick's disease. Additionally, the following criteria can be used to diagnose patients:

Behavioral change is the most common presentation and will affect up to 90% of Pick's disease patients.

Personality changes are a distinguishing characteristic of Pick's disease.

- Development of behavioral or cognitive deficits manifested either by early and progressive change in personality or early and progressive loss of language function
- The behavioral or language deficits cause significant impairment in social or occupational functioning and represent a significant decline from the previous level of functioning
- The course is characterized by gradual onset and continuing decline
- Deficits are not due to other nervous system conditions, systemic conditions, or substance abuse
- Deficits do not occur exclusively during delirium
- The disturbance is not better accounted for by a psychiatric diagnosis such as depression.

As with Alzheimer's disease there is no cure for Pick's disease. Likewise, treatment emphasizes symptom management but, because of the rarity of the disease, there is little evidence-based guidance. Medicines used in the treatment of Pick's disease focus on neurotransmitter replacement. *In-vitro* evidence suggests decreased serotonin binding and low serotonin levels in the frontal cortex. In fact, there are isolated small clinical trials showing symptomatic improvement using SSRIs, including fluvoxamine, fluoxetine, paroxetine and sertraline. Some patients may require antipsychotics, although they should be used carefully since some patients may also have Parkinson's disease. In contrast to Alzheimer's disease, there is no role for cholinergic drugs in Pick's disease.

In summary, Pick's disease is a rare degenerative type of dementia. Unlike Alzheimer's disease, it does not affect cognition and normally occurs in a younger population. Its symptoms are usually a combination of extreme behavioral changes and aphasic symptoms. Pick's disease, like all dementias, is extremely difficult for family members and loved ones to cope with. Because it is terminal, diagnosis can be devastating. Because of its duration and bizarre swings in personality loved ones may feel alienated and must be educated to the facts about the disease. Healthcare providers are only able to treat symptoms of the disease. A confirmed diagnosis, while difficult, is crucial in properly treating the symptoms of Pick's disease.



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Meet our Certified Geriatric Pharmacists!

The Certification in Geriatric Pharmacy (CGP) is a certification that may be earned by any pharmacist that indicates specific knowledge of the following in the elderly: common disease states, biologic differences in the elderly patient, medication interactions and medication side effects. A Certified Geriatric Pharmacist has taken and passed an exam that shows this knowledge and is required to take specific continuing education courses to keep current on geriatric issues. A major goal of this certification is to identify the numerous medication related problems that are preventable – in the geriatric patient that is often prescribed a large number of medications due to multiple disease states.

The following Neil Medical Group Pharmacists have the CGP certification:



Crystal Chandler
Lori Edwards
Heather Eaton-Erskine
Steve Godfrey
Bobbie Hall
Wendy Holmes
Mike List
Michelle Merritt
Robert Smith



For more information on the Certified Geriatric Pharmacist program or to apply for certification, please visit www.ccgp.org.

Pharm Notes is a bimonthly publication by Neil Medical Group Pharmacy Services Division. Articles from all health care disciplines pertinent to long-term care are welcome. References for articles in Pharm Notes are available upon request. Your comments and suggestions are appreciated. Contact:

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