Without the liver, we would not be able to metabolize some components of the food, drinks, and medications that we eat; there would be problems in hemostasis and we would not be able to properly digest the food that we eat, particularly fatty ones. These are only a few among the many contributions of the liver to homeostasis. However, there are also a lot of factors that can bring damage to the liver. Although the pathogenesis of liver diseases are most likely caused by a combination of a lot of factors, there have been well-studied disorders where genetics play the most crucial role in initiating disease. An example of which is alpha 1 antitrypsin deficiency.

Overview: Alpha 1 Antitrypsin

Biochemistry
Alpha 1 antitrypsin is a **single-chain glycoprotein that is produced by the hepatocytes, phagocytes and epithelial cells of the lungs**, the predominant producer among which is the first. It is made up of a chain of 394 amino acids that demonstrate various glycoforms. It has a mass of 52 kDa and belongs to a superfamily of proteases called **serpins**. It is said to be the most prominent among the protease inhibitors in the group.

Serpins are a group of proteins that consists of proteins with similar structures as that with alpha 1 antitrypsin. These are known to irreversibly inactivate chymotrypsin-like proteases by causing a conformational change in the structure of the protease, thereby inhibiting the binding of its active site with its ligands.

The term ‘serpin’ is actually an abbreviation for ‘**serine protease inhibitor**’.

The gene that is responsible for the expression of alpha 1 antitrypsin is found on **chromosome 14** and is characterized to be very **pleomorphic**. In fact, there are at least 75 alpha 1 antitrypsin expressing genes known currently. The most common of which is the **PiMM**, with the abbreviations ‘Pi’ and ‘MM’ denoting ‘protease inhibitor’ and the genotype of the 2 alleles of an individual respectively. PiS variants produce a moderately lower amount of alpha 1 antitrypsin in the serum while Pi-null does not produce any at all. Reduction in alpha 1 antitrypsin production caused by these variants does not necessarily cause manifestations in the person having them.

**Protective functions**

Alpha 1 antitrypsin is known to inhibit the action of many serine proteases. These include **neutrophil elastase, cathepsin G** and **proteinase 3**. These proteases are usually produced by neutrophils during inflammatory processes. An absence of alpha 1 antitrypsin is known to have deleterious effects on the **liver** and lungs.

**Alpha 1 Antitrypsin Deficiency**
Conditions Associated with Alpha-1 Antitrypsin Deficiency

- Skin:
  - Necrotising Panniculitis
  - Systemic Vasculitis
  - Psoriasis
  - Urticaria
  - Angioedema

- Lungs:
  - Chronic Obstructive Pulmonary Disease (Panacinar Emphysema)
  - Bronchiectasis
  - Asthma

- Liver:
  - Cirrhosis
  - Neonatal Hepatitis
  - Hepatocellular Carcinoma

- Kidneys:
  - Proliferative Glomerulonephritis
  - IgA Nephropathy

- Intestines:
  - Inflammatory Bowel Disease

- Vascular:
  - ANCA-positive Vasculitis
  - Abdominal and Intracranial aneurysms
  - Arterial fibromuscular Dysplasia

Epidemiology

Image: “European distribution by country of genotype PiSZ — heterozygous alpha 1-antitrypsin deficiency.” by Olve Utne. License: CC BY-SA 2.5
The first time alpha 1 antitrypsin deficiency was diagnosed in an adult patient in 1963. It was first known to be occurring in patients with emphysema. Later on, it was also observed to occur along with liver disease and was first discovered on neonates with liver problems early on.

Although it has a significant prevalence of the various populations in the world all over, it is observed to be more prominent among Caucasians of European descent. It occurs in almost 1 out of 1600 to 2000 live births and is the most common genetic causative factor for juvenile liver problems.

In fact, most children requiring liver transplantation are the ones diagnosed with alpha 1 antitrypsin deficiency.

Many epidemiologic studies related to alpha 1 antitrypsin deficiency have been performed and are still underway. Although certain problematic variants of the alpha 1 antitrypsin gene may cause some degree of alpha 1 antitrypsin deficiency, it is found out that not all cases develop a significant liver disease. This goes to show that even in a genetic condition, environmental factors may still play a crucial part for the disease progression.

Etiology and Pathogenesis

The most commonly known genetic mutation associated with clinically significant alpha 1 antitrypsin deficiency is that of the PiZ variant. Individuals having 2 copies of the Z allele are known to exhibit clinical manifestations as only up to 10 % of the needed functional alpha 1 antitrypsin are produced. The same manifestations could also be present in homozygous individuals having the PiMZ variant because the allele acts dominantly and does not need a duplicate allele copy to exert its effects. Some patients with clinically manifesting alpha 1 antitrypsin deficiency may also have the PiS variant.

This disorder can present early in life and is frequently diagnosed among young children and infants showing liver problems.

The mutation in the gene is demonstrated to cause an abnormal folding of the alpha 1 antitrypsin protein. The resulting abnormality in structure leads to an impairment in the mobility of the glycoprotein out from the secretory cell such as the hepatocytes. A single amino acid replacement (Glu342 to Lys342) in the chain is said to be the problem. The defective protein, called alpha 1-AT Z is then retained and accumulated in the endoplasmic reticulum as it fails to move on to the Golgi apparatus. A deficiency of the glycoprotein follows this.

Aside from the impaired production of alpha 1 antitrypsin in the sera, point mutations in the gene ultimately lead to the damage of hepatocytes as the accumulated alpha 1-AT Z polymerizes and aggregates to cause liver inflammation. This gain-of-toxic mechanism also predisposes the individual to liver cancer as mitochondria tend to lose their function as hypothesized by many researchers.

As already mentioned, environmental factors play a key role in the development of the disease. This is because certain exogenous factors actually affect the intracellular mechanisms that attempt to eliminate the aggregated alpha 1-AT Z in the cells producing these defective proteins.

Mutations in the pathways that can somehow alleviate the alpha 1-AT Z aggregation intracellularly have also been implicated in the development of the disease. For instance,
single nucleotide polymorphisms in the downstream flanking region of the endoplasmic reticulum mannosidase I can significantly affect the degree of alpha 1 antitrypsin deficiency and liver damage present. This pathway is one of the many that compose the intracellular clearing pathways for defective alpha 1 antitrypsin proteins.

Clinical Manifestations

Liver

Most if not all of the clinical presentations of alpha 1 antitrypsin deficiency result from a general impairment of the functions of the liver. It is diagnosed early in childhood and can manifest as early as the first 2 months of life. However, cases have been found where signs and symptoms start later in childhood, teenage years or even adulthood. Infants and young children may demonstrate various signs of impaired vitamin K synthesis such as bleeding at the:

- Umbilical stump
- Gastrointestinal tract
- Intracranial space

Unexplained bruising may also be evident. Other signs such as failure to gain weight may also be visible. A condition called neonatal hepatitis with cholestatic jaundice may also be present in some newborns with alpha 1 antitrypsin deficiency. Newborns with this condition tend to go through acute bouts of hepatitis with complete recoveries in between. However, there are also instances where newborns enter an episode of acute hepatitis and fail to bounce back. These cases usually progress to acute hepatitis.

As the affected individual progresses to later years, signs and symptoms of the advanced liver disease may show up. This may include:

- Hepatomegaly
- Splenomegaly
- Ascites
- Bleeding esophageal varices
- Scleral icterus

These manifestations are usually associated with cirrhosis among adults. In some cases, especially with individuals with the PiZZ genotype, hepatocellular carcinoma may develop, although not always in the setting of cirrhosis. There is still insufficient data about the ability of heterozygous genotypes to cause alpha 1 antitrypsin deficiency. However, there are some studies showing that individuals with the PiSZ gene can show clinical manifestations. This is said to be because of its resemblance to the PiZZ gene.

Effects on the lungs and other systems
Alpha 1 antitrypsin deficiency is the most common genetic cause of emphysema. However, this type of emphysema comprises only a small part of all the cases of emphysema. The onset of manifestations of alpha 1 antitrypsin deficiency in the lungs usually starts at the 3rd or 4th decade of life. Clinical presentation starts with coughing, difficulty with breathing and expectoration.

As mentioned a while ago, external factors such as occupational exposure to irritants and smoking accelerate the progression of the disease. These factors even reduce the median survival of alpha 1 antitrypsin deficiency affected individuals by 20 years or more. Individuals with the PiS variant are even more subjected to pulmonary complications compared to those with PiZZ.

Other inflammatory diseases associated with alpha 1 antitrypsin deficiency include:

- Necrotizing panniculitis
- Wegner's granulomatosis
- Membranoproliferative glomerulonephritis
- IgA nephropathy
- Other vasculitis syndromes

Pathologic Changes in the Liver

When viewed under the microscope, a liver biopsy sample can show cytoplasmic globular inclusions in hepatocytes. These round to oval-shaped inclusions stain magenta on when using an eosin and hematoxylin. These are also periodic acid-Schiff (PAS)-positive and diastase resistant. These inclusions represent the accumulated mutant alpha 1-AT z proteins.

During the early stages of the disease, these inclusions are mostly found in the periportal liver cells. This goes to show that disease progression tends to follow a peripheral to central direction. The presence of these inclusions in the hepatocytes does not, however, correlate with the severity of the disease in all cases.

In samples coming from neonates and infants with the PiZZ variant, changes in the
hepatocyte may vary. Especially in very early cases, PiZZ alpha 1 antitrypsin deficiency may present with hepatitis accompanied with cholestasis and fibrosis. Some infants may show the only steatosis.

**Differential Diagnosis and Diagnostic Investigation**

In all cases where there are signs and symptoms of abnormal liver functioning such as elevated transaminases and prolonged clotting and bleeding times, alpha 1 antitrypsin deficiency should always be considered. Differential diagnoses may vary among different ages.

<table>
<thead>
<tr>
<th>Age</th>
<th>Causes</th>
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<tbody>
<tr>
<td><strong>Infancy</strong></td>
<td>- Extrahepatic biliary atresia</td>
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<td></td>
<td>- Alagille syndrome</td>
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<td>- Cystic fibrosis</td>
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<td>- Choledochal cyst</td>
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<td>- Galactosemia</td>
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<td>- Tyrosinemia</td>
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<td>- Neonatal giant cell hepatitis</td>
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<td>- Progressive familial intrahepatic cholestasis</td>
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<td>- TORCH infection</td>
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<td><strong>Childhood/Adolescence</strong></td>
<td>- Autoimmune hepatitis</td>
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<td>- Wilson’s disease</td>
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<td>- Infectious hepatitis</td>
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<td>- Toxic hepatitis</td>
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<td><strong>Adulthood</strong></td>
<td>- Wilson’s disease</td>
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<td>- Autoimmune hepatitis</td>
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<td>- Hepatocellular carcinoma</td>
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<td>- Hemochromatosis</td>
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<tr>
<td></td>
<td>- Cryptogenic cirrhosis</td>
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<td></td>
<td>- Nonalcoholic steatohepatitis</td>
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</table>

(Table adapted from Textbook of Clinical Gastroenterology and Hepatology, 2nd ed. by Hawkey CJ, Bosch J, Richter JE, Tsao GG and Chan FKL)

Diagnosis of alpha 1 antitrypsin deficiency can be confirmed by measuring serum levels of alpha 1 antitrypsin and determining the PI type by isoelectric focusing gel electrophoresis. Abnormal results will show around 10—15 % of the normal levels of alpha 1 antitrypsin in the blood.

Being an acute phase reactant, alpha 1 antitrypsin may also be elevated in the presence of inflammatory processes. This means that an elevated serum measurement should not be used as a sole basis for the exclusion of alpha 1 antitrypsin deficiency.
Although not necessary, a liver biopsy can help in determining the extent of liver damage and the presence of hepatocellular carcinoma. The presence of PAS-positive and diastase-resistant inclusions is diagnostic of the disease.

Treatment and Prevention

The definitive treatment for alpha 1 antitrypsin deficiency, especially for advanced cases is liver transplantation. For milder forms or in the early stages of the disease, supportive treatment is indicated.

Oxidative stress to the hepatocytes and bile stasis are prevented by giving vitamin E and ursodeoxycholic acid respectively. However, studies have shown that these two treatments do not exhibit efficacy for their indications. Other treatments such as gene therapy and the use of pharmacologic chaperones are already being developed.

Health education plays an important part in the treatment regimen for alpha 1 antitrypsin deficiency. It should be emphasized to patients with the disease that smoking will aggravate their condition and can cause fatal consequences.

For patients with lungs as the predominantly affected organ, replacement therapy with plasma containing alpha 1 antitrypsin is usually indicated. Lung transplantation may also be indicated for these patients, especially those with advanced lung involvement.

Complications and Prognosis

Usually, liver involvement in alpha 1 antitrypsin deficiency progress slowly but can be accelerated in the presence of comorbidities and infections. Manifestations develop into severe forms much like that with other chronic liver diseases. Other complications include severe bleeding, especially among newborns, and malnutrition as a result of poor food intake and malabsorption brought about by cholestasis.

Since not all individuals with the homozygous gene variant present with signs and symptoms, it is important to understand that patients with alpha 1 antitrypsin gene variants can continue life without any liver-related complications. For advanced cases, liver transplantations have demonstrated favorable results.

Review Question

The correct answer can be found below the references.

Which of the following histopathologic findings is diagnostic of α1-antitrypsin deficiency?

- A. PAS-positive and diastase-resistant inclusion bodies
- B. Mallory bodies
- C. Ground glass appearance of liver cells
- D. Intracellular fat inclusions

References


**Correct answer:** A

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