What else could it be? Alpha-1 antripsin deficiency

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Introduction

Alpha-1 antitrypsin deficiency (AATD) is a hereditary condition caused by one of many mutations in the SERPINA1 gene, resulting in reduced levels or absence of the alpha-1 antitrypsin (AAT) protein. AAT is produced in the liver and plays a vital role in protecting lung tissue from damage by neutrophil elastase, an enzyme released during inflammation (as a response to smoking tobacco or cannabis).

When AAT is absent or dysfunctional, the balance between the proteases and their inhibitors is disturbed. Over time, this predisposes individuals to premature emphysema and, in some cases, liver disease due to the accumulation of misfolded protein in hepatocytes.

Although AATD is one of the most common inherited metabolic disorders in northern Europe (affecting around 1 in 2000–5000 people), it remains underdiagnosed. Fewer than 10% of affected individuals are thought to have been identified, partly because many individuals may not have symptoms, or they overlap with common conditions such as COPD and asthma.

AATD: key points for primary care professionals

by Vince Mak

Q1: In a patient with an established diagnosis of COPD or emphysema, when should we suspect AATD and how do we test for it?

Suspicion should be raised in the following situations:

- Early onset disease: COPD or emphysema diagnosed before age 45–50 years.
- Minimal smoking history: significant emphysema in a patient with <10 pack-years of smoking.
- Atypical distribution on imaging: basal predominance (in contrast to the usual apical pattern of smoking-related emphysema).
- Family history: relatives with emphysema, liver disease or known AATD.
- Unexplained liver disease: especially in adults with coexistent lung disease.

Testing:

1. Serum AAT level – a simple blood test, but levels can be misleading if taken during an acute illness (as AAT is an acute phase reactant).
2. If levels are low or borderline, order genotyping for the SERPINA1 alleles (used to be phenotyping, which detected the specific mutated protease inhibitor (Pi) protein) eg, MM, ZZ, SS or combination. Many labs now offer reflex testing if the levels are low.
3. Interpret results in context – remember that the 'protective threshold' for AAT is about 0.6 g/L; patients with levels below this are at significantly increased risk.

Most guidelines recommend that all patients with COPD or emphysema should be tested at least once for AATD, regardless of smoking history.

Q2: How important is a smoking history in contributing to emphysema in AATD?

Smoking is critically important.

- In AATD, the deficiency of protective anti-elastase activity means that cigarette smoke accelerates lung tissue destruction far more than in the general population.
- A smoker with ZZ genotype may develop severe emphysema in their 30s or 40s, whereas a never-smoker with the same genotype might remain relatively well until much later in life.
- Even heterozygotes (eg, MZ, MS) have a higher risk of COPD if they smoke.

Key clinical message

Absolute smoking cessation is the single most effective intervention in all forms of AATD. It is vital to emphasise this to patients and provide robust smoking cessation support.

Q3: Are there any other signs, symptoms or investigations we should do in a patient with AATD?

Respiratory:

- Presenting symptoms may mirror COPD: breathlessness, cough and wheeze.
- Asthma-like features are sometimes seen, but airflow limitation is usually less reversible.

Hepatic:

- Because abnormal AAT protein accumulates in hepatocytes, patients are at increased risk of liver disease, including cirrhosis and hepatocellular carcinoma.
- Consider simple liver function tests at baseline, especially if symptoms suggest hepatic involvement.

Other features:

- Some patients develop panniculitis (painful skin nodules, rare but characteristic).
- Family history may reveal relatives with unexplained emphysema or liver disease.

Investigations:

- Spirometry (as for any COPD patient) to detect obstruction, and gas transfer to detect emphysema.
- Chest CT if available: panacinar emphysema, typically lower lobe-predominant, is highly suggestive.
- Liver ultrasound and bloods may be appropriate if liver involvement is suspected.

Q4: How do we treat a patient with AATD and emphysema?

There is no specific treatment for AATD. Core management is standard COPD care, but with additional considerations:

- Smoking cessation (tobacco and cannabis) should be the highest priority.
- Vaccination: influenza and pneumococcal vaccination should be up to date.
- Optimised inhaled therapy: bronchodilators and inhaled corticosteroids according to usual COPD guidelines.
- Pulmonary rehabilitation.
- Oxygen therapy: if hypoxaemia develops, assess according to standard criteria.
- Lung volume reduction procedures and transplantation are other options for treatment, as in other cases of severe COPD.
- Augmentation therapy: intravenous AAT replacement is available in some countries for patients with severe deficiency (usually ZZ, SZ or Null genotypes) and airflow obstruction despite optimal care. The NHS does not commission this since there is limited trial evidence that it is effective in improving meaningful outcomes such as lung function, quality of life or exacerbations. However, patients may be enrolled in clinical trials or specialist programmes.
- Liver disease management involves standard hepatology referral; no role for AAT augmentation.

Q5: When should I refer a patient with AATD?

Referral to secondary or tertiary care is appropriate in several situations:

- Confirmed deficiency (especially ZZ, SZ or Null alleles).
- Young patients with COPD.
- Consideration of lung volume reduction or transplantation.
- Consideration of augmentation therapy (specialist centres only).
- Evidence of liver disease requiring hepatology assessment.
- Family testing and genetic counselling with confirmed homozygous genotypes or severe deficiency.

In practice, most patients with a confirmed AATD genotype benefit from at least one specialist consultation to guide long-term follow-up.

Q6: How should I counsel a patient with AATD?

Counselling is a critical aspect of care. Patients often feel anxious when first told they have a genetic condition.

Points to cover:

- Nature of the condition: "This is a hereditary condition where your body makes less of a protective protein

called alpha-1 antitrypsin. That makes your lungs and liver more vulnerable to damage."

- Absolute smoking avoidance.
- Avoid occupational dust/fumes if possible.
- Moderate alcohol use to protect the liver.
- Family implications: offer testing to first-degree relatives.
- Monitoring: regular lung function tests and liver checks if needed.
- Refer patients with homozygous disease for genetic counselling
- Support resources: direct patients to the Alpha-1 UK Support Group or other charities for peer support.
- Reassure patients that with modern care, many live full and active lives, particularly if they do not smoke.

The chances of an individual passing on carrier status or AATD to their children are shown in the table.

	Partner normal (MM)	Partner carrier (eg, MZ, MS, etc)
Patient with AATD (ZZ, SS, etc)	All children will be carriers No children will have AATD	Each child has a 1 in 2 chance of having either AATD or being a carrier
Partner carrier (eg, MZ, MS, etc)	No child with AATD Each child has a 1 in 2 chance of being a carrier	Each child has a 1 in 4 chance of having AATD Each child has a 1 in 2 chance of being a carrier

Summary for primary care

- Test all COPD and emphysema patients once for AATD — especially if young, non-smokers or with unusual patterns.
- Smoking cessation/avoidance is the most important intervention.
- Consider liver involvement.
- Treat as per COPD guidelines.
- Refer confirmed cases to a respiratory specialist for further guidance.
- Counsel patients and families sensitively and signpost to support.

With these steps, primary care has a vital role in reducing the impact of this genetic condition and supporting patients to maintain long and active lives.

What does AATP mean for the patient?

Let's hear from Neil Jackson (a PCRS patient representative)

Q1: What is thebackground and story around my being diagnosed with AATD?

It's winter 2008/09. I'm 45, a year off cigarettes. My habit was 20–30 a week, often for cannabis, not heavy but probably risky because of how I smoked. After a Christmas cold I developed a cough and wheeze that wouldn't shift. My wife pushed me to visit the GP. He confirmed the wheeze, ordered bloods, chest X-rays and mentioned diabetes, thyroid issues and high liver enzymes despite my barely drinking.

X-rays showed nothing except very large lungs (I'm 6'6" and needed three plates). After being referred for spirometry, I was told not only did I have COPD (something I'd never heard of) but, worse, it was emphysema – something I thought only coal miners got. With a newborn son at home, I felt I was on borrowed time. The stigma of a 'smoker's disease' a year after quitting felt cruel.

The consultant explained that because I was young for emphysema, they'd test for something with a Star Trek name. Weeks later, after a holiday tag with my GP, I was told I had the PiZZ form of alpha-1 antitrypsin deficiency (AATD), the worst of the common types.

It's been a steep learning curve, and now I know only too well what AATD is. My GP admits I know more than he does now, but we continue to learn together.

Despite the shock, I consider myself lucky. My diagnosis was unusually fast – just three months from first consultation to confirmation. Most 'Alphas' wait seven years, often misdiagnosed with asthma.

Q2: What impact has it had on me and my lifestyle?

Exercise was never my strength – I'm tall, thin and unsporty – but by my late thirties it was harder still. Breathlessness, fatigue and malaise crept in. Living at the top of a Georgian townhouse meant 90 steps daily. I measured my fitness by whether I could beat the ceiling light timer to the next switch.

Eventually, I had terrifying dyspnoea attacks: minutes of drowning-in-sand suffocation. They convinced me exercise was unsafe. I stopped pushing myself, avoided going out and narrowed my life to home where I felt safe with my wife and newborn son. My world shrank. I leaned more on my wife while trying to look like a normal 40-something.

Q3: What have I done/need to do to manage it effectively?

The first step was acceptance. Denial didn't suit me. I forced myself to learn about AATD, where it hits, and what I could do. Pulmonary rehabilitation (PR) initially worried me – I expected to be the youngest there – but encouragement from other patients persuaded me. I went and was an instant convert.

I discovered exercise wasn't the risk but the remedy. Dyspnoea doesn't come from exercise; it comes from lack of it. By building muscle tone, I eased strain on my body. The hardest part was ignoring my brain's warnings to rest and doing the opposite. But, over time, movement reduced the breathlessness and restored some hope.

AATD is incurable and progressive, but it needn't mean surrender. With knowledge, rehabilitation and persistence, I found a way to push back and live actively. Maybe not doomed after all.

Q4: What support do Alphas need from primary care?

At diagnosis, patients often can't hear much – "progressive and incurable" is overwhelming. Be ready to follow up and explain things in stages. Point them to the Alpha-1 UK Support Group, but know it may take time before they can absorb information.

If you're not fully confident in the genetics, don't wing it. Too many patients hear confusing things like "you're just a carrier, you'll be fine" (not always true) or myths such as "it only passes through the female line". Use proper pheno- or genotyping, not just serum levels, which can fluctuate. Make sure patients understand results, risks and what they mean for their family. Arrange genetic counselling, but don't force it on day one; family guilt and resistance can complicate matters. Sometimes full testing isn't even needed if parental genotypes make the child's status clear.

Create self-management plans and ensure patients understand them. Remind them it's not an instant death sentence. With support, exercise and strict avoidance of smoking, many can live long, rewarding lives.

Check patients annually with spirometry and regularly with liver scans – even carriers. Vaccinate them (and their families) against pneumonia, flu and COVID. Provide an antibiotic rescue pack for exacerbations, with clear instructions on when and how to use it. Be mindful when prescribing – their livers are vulnerable. Even routine drugs like terbinafine can be risky. Encourage patients to ask about contraindications.

PR should be arranged as early as possible, with repeats if needed. If available, refer to local "Healthwise" schemes or similar exercise programmes. Personally, my subsidised weekly circuits session has been the single biggest boost to my health, resilience and mental outlook.

Refer patients to NHS Alpha-1 clinics but stay involved – don't abandon them. Clinics can be far away and intimidating, but with GP support alongside, patients can manage much better.

Finally, empower them to be vigilant – Alphas are their own canaries in the coal mine. They need to know they can alert you to changes and be heard quickly. With consistent support, Alphas can expect a decent future.