

Patient voice

The patient perspective of alpha-1 antitrypsin deficiency: disease burden and unmet needs

Introduction

Alpha-1 antitrypsin deficiency (AATD) is one of the most frequent rare diseases in Europe and may result in serious lung disease and/or liver disease in adults. People with this condition have a much lower level than normal of the protective protein alpha-1 antitrypsin (AAT) in their blood. AAT protects the body from a powerful enzyme called neutrophil elastase. AATD is an inherited condition that is caused by mutations in the *SERPINA1* gene, which can lead to a shortage of AAT or an abnormal form of the protein that cannot control neutrophil elastase. The *SERPINA1* gene has more than 100 variants, coded for by two alleles (different versions of the same gene). PiMM is the normal allele, while PiMZ has one normal and one defective allele and PiZZ is the most common allele that causes AATD. The signs and symptoms of the condition and the age at which they appear vary significantly among individuals. The heterogeneity of the clinical picture of AATD depends on a variety of genetic and external aspects. Environmental factors, such as exposure to tobacco smoke, chemicals and dust, probably impact the severity of AATD-associated lung disease.

Treatment for AATD-associated lung disease includes inhaled medications, immunisation against respiratory viruses, antibiotics to treat acute respiratory infections, supplemental oxygen and exercise. The only disease-specific treatment for AATD-associated lung disease is intravenous

augmentation therapy, which contains AAT protein from purified human blood plasma. The American Thoracic Society/European Respiratory Society AATD statement (2003) [1] has been widely regarded as the most comprehensive guidelines for the management of ATTD in Europe and the USA. Since it was published, extensive research efforts have been underway to develop novel, effective treatments for the disease; however, no novel therapies have been licensed yet.

In this article, three people with AATD from Germany, the UK and Belgium share their experiences of living with this rare, genetic condition. They reflect on their situation and perspective regarding the burden of AATD, the impact of the condition on different aspects of their and their families' lives, available treatment options and their hopes for how living with AATD could be improved.

Three AATD patient stories from across Europe

Marion Wilkens has AATD and lives in Germany

Receiving the AATD diagnosis, in my case when I was 40 years old, was a hard blow (figure 1). My doctor had a strong suspicion (that is why he carried out the test) but gave me no information about the disease – everything was just terrible.

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Three people with alpha-1 antitrypsin deficiency (AATD) share their experiences of living with this rare, genetic condition. They reflect on living with AATD and its impact on their lives including inequity of access to treatment across Europe. <https://bit.ly/3rrYS9s>



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Figure 1 Marion Wilkens.

To start at the beginning: I was diagnosed with asthma at the age of 20, my doctor called it “stress asthma”. Since then, I have seen a pneumologist once a year for a check-up and received a corticosteroid spray as well as an emergency spray (to widen the airways). I continued to smoke because I believed, like so many young people, that nothing could knock me down. Aged 30 I finally quit smoking, succeeded with my first attempt and remained steadfast.

My first symptoms were coughing, but also everyday signs, such as difficulties with breathing when tying my shoes or being short of breath when walking up the stairs. All this even though I did a lot of sport and even financed my studies by teaching aerobics and other fitness sports.

When I was 40 years old, my doctor said that the problems caused by smoking should no longer be felt because the lungs can regenerate a bit and my asthma was well adjusted. My lung function values, however, said something else: my FEV₁ was not very high and the other values had also become worse. My doctor asked if he could do a blood test, and 3 weeks later I received the diagnosis “Alpha-1-Antitrypsin Deficiency” with a serum level of 0.22 mg·dL⁻¹ and a PiZZ genotype, and a doctor who knew very little about the disease. So, I went home very confused!

I started to inform myself. The internet gave me some information, but not all of it was correct, as I know today. I was afraid that I would not accompany my two children to adulthood. Now, I know that you do not necessarily die early and there are many things you can do to positively influence the progression of the disease. Treatments like augmentation therapy are fortunately available and paid for by our healthcare system here in Germany. But other therapies are also important, for example rehabilitation, lung sports (undertaken once or twice a week with instructors specially trained in helping lung patients to exercise), breathing therapy, balanced nutrition, and vaccinations.

For me, it was very important to master breathing techniques, to manage breathlessness in an emergency and to learn techniques to keep my chest free of mucus (through respiratory therapy and/or exercise). Keeping active in everyday life, muscle-strengthening exercises and maintaining or improving endurance has also been very important to me as well as maintaining a healthy weight and balanced diet. I aim to maintain some fat reserves, but every gram must also be moved, which is exhausting for my lungs, it is a difficult balance to maintain.

It is important for everyone to invest in their health and we “Alphas” need a little more time for this. I do about half an hour of training per day, plus one hour each of respiratory therapy and lung sports once a week.

I was also very concerned about my two kids. Didn't the doctor say it was a genetic defect? Have I passed it on? Since the youngest was only 2 years old, we first tested my husband: PiMM (*i.e.* not a carrier of AATD) – fortunately! So, as long as they do not smoke, our two children are not particularly at risk of developing symptoms due to AATD. Further family screening revealed many PiMZ individuals in the family, but no other family members with PiZZ.

Being affected by a rare disease that is not visible makes it difficult to explain to others. I found excuses as to why I do not ride a bike but drive a car, and for a long time I told only a few people about the condition and what it means to me. Today I talk about my disease with everyone who listens, I have learned a lot about it, and I know that it helps to talk about it and to mention our disease to others.

I found comprehensive information and help at the patient organisation in Germany. Today, I am the chairwoman of Alpha1 Deutschland e.V. and try to help as many Alpha-1 patients as possible to overcome their fears, manage their treatments effectively and make their daily lives easier for them and their relatives.

Michael Bartlett has AATD and lives in England, UK

When I was diagnosed with AATD at the age of 35 years, it came as a big shock (figure 2). I had started to notice that I was getting breathless and put it down to gaining a bit of weight, being an ex-smoker and not getting enough exercise. But when I realised I was getting more and more out of breath at my work with a local construction firm and feeling exhausted walking up the stairs at home, I knew something was wrong.

My GP (general practitioner) thought my symptoms were probably caused by asthma and I was given a blue inhaler. After a few months with no improvement, I was convinced that I had lung cancer. Following a spirometry test, which showed my lung age in three figures, I was referred to my local hospital where a chest physician very quickly



Figure 2 Michael Bartlett.

made the AATD diagnosis following a blood test. I was told that I had the ZZ phenotype, which means I have a very low level of AAT in my blood.

This was a whirlwind time for me: I went from thinking that I had a treatable condition (asthma) to being told that there was limited help for me and that a lung transplantation was likely to be my only option. I didn't know what to think. Over time, I have learned that a lung transplantation is not a cure but a temporary measure that may give you a decent quality of life for a limited period. There is no specific treatment for AATD available in the UK, and that is the really difficult thing. At the time I was diagnosed, my two boys were just 7 and 5 years old; both very active, running around the garden, swimming and cycling. These were all things that I could no longer participate in and it was very depressing sitting on the side-lines, watching other people doing what I should have been doing.

6 years after I was diagnosed, I failed my oxygen assessment and my working life was over. My workplace was very understanding, but the financial implications of no longer being the major breadwinner were worrying and it had a massive impact on my marriage, future, everything. Luckily, my wife is an MM and the boys are MZs so hopefully, as long as they keep healthy and live a decent lifestyle, they should be fine.

Mentally, it was very difficult to go out with oxygen tubing strapped around my face every day. It is something you expect older people to be doing, not someone of my age. To start with, I found it

very embarrassing, and it was very difficult for me knowing that my kids and wife had to see me like this. I wondered what do they think of me now?

I've got more used to this over time, but I can't leave home without oxygen and I struggle to do the simplest of things such as walking, eating and showering. Things declined for me after I left work, and now I have a stairlift, mobility scooter and could not get by without my oxygen. I am really considering lung transplantation now. I have had a double lung assessment and if it had not been for COVID-19, I may well have taken the plunge already. I have a lot of fear, I worry about the scarring and the responsibility I would feel post-transplant to the donor's family and the need to make a success of it. The operation itself and the post-care of a double lung transplant is massive, not just on the patient but on those around them. It is not the golden ticket I thought it was when I first came into this.

When you first get your diagnosis, the care is fantastic but once you have been given information about how to alleviate your symptoms, then there is not much new information – or hope – coming from any direction. You are pretty much left to get on with it. Living with no hope is a difficult thing.

This is quite sad, and augmentation therapy, which is available to some people with AATD in some countries in Europe, the USA and beyond, is not available to those of us living in the UK. Although clinicians have varying views on its effectiveness, it does seem to have some impact in preventing the speed at which this condition advances. AATD comes into the rare disease category and patient advocacy groups such as the Alpha-1 UK Support Group are doing some incredible work to put our case forward and to raise awareness.

For me, it is too late as there are cut-off points for the level of deterioration where this therapy will benefit you and so I probably would not be eligible for it now. But we will keep trying and the patient support groups will keep trying. I have made a lot of friends over the years and there are a lot of people who have gone on this journey with me, and also a lot of people who sadly are not with us anymore.

I do believe that, in years to come, there will be more awareness of AATD. There is a lot of inequality across European countries regarding availability of augmentation therapy. In my eyes, every illness warrants treatment, and the cost of this therapy for the niche group that need it would be a drop in the ocean compared to the money that is being spent elsewhere. For all those future generations of "Alphas" coming along, we have got to try and make sure that universal provision of augmentation therapy does not keep getting dismissed in the way it has been.

Frank has AATD and lives in Belgium

I was diagnosed with AATD by accident at the age of 45 years (figure 3). My doctor did not look for antitrypsin, but she selected "electrophoresis"

(serum protein blood test) on the laboratory requirement form accidentally.

At that time in my life, I just had lost my left arm due to an infection and had no time to care about my new genetic condition. It was more important to learn how to dress myself with one hand, how to eat, how to take a shower and how to drive my adapted car. Also, I did not suffer from liver problems or lung problems. So, I forgot about AATD for about 10 years, and then, on a sunny weekend in March 2008, suddenly I became curious and had a lot of questions: I wanted to know more about my “genetic makeup”. I consulted geneticists, visited lung doctors and finally started augmentation therapy when I had developed more respiratory symptoms. After 12 years I am still on treatment, my lungs are stabilised and in good condition, I can avoid exacerbations like bronchitis or pneumonia – I feel lucky!

However, AATD has changed my life completely. I have to look after my health, so I make sure I get enough sleep and each morning I ride for half an hour on my home exercise bike, eat a fresh salad breakfast, with tea and wholegrain bread. My regular treatment sessions in hospital and medical examinations have high priority and are time consuming.

We have no homecare service available in Belgium for the administration of augmentation therapy, so I get my infusion of antitrypsin in the day clinic. This means that I regularly come into contact with immunosuppressed people on oncological treatment and am exposed to the risk of infections such as COVID-19 and flu. When I leave the hospital, I am always a bit dizzy, sometimes with a headache, due to the protein shock. All in all, it takes me half a day to recover.

Since 2013, I often travel to meet other “Alphas” and medical experts and have built up a social life in the patient community and have helped to establish and assist others in different countries to set up local Alpha-1 patient associations. I have met extraordinary people and have made new friends.

To live with a rare disease has taught me to handle risks differently. So now, I go for regular

vaccinations and avoid COVID-19 by staying at home or wearing a mask. But also, a new, more responsible approach guides my daily life: by being healthy and in the best shape I can be, I am able to support newly diagnosed “Alphas”, to educate carriers, and to support and contribute in the wider Alpha-1 community.

The way I value health has changed to another dimension. I am curious about life, I laugh a lot, dance as I like to, cry if I am deeply touched by simple things like a flower or an abstract painting. To be aware of and to live with my condition has opened up new horizons to me, full of unexpected moments of sensations, of happiness, new contacts! I feel very grateful about that!

However, Alpha-1 patients are not always lucky! Unfortunately, the Belgian Health Commission stopped reimbursement for newly diagnosed “Alphas” in 2010; so, augmentation therapy is no longer available to new patients as it has been for me. I met other “ZZ-Alphas” in Belgium, who needed augmentation therapy but could not get reimbursed, so we launched a Belgian not-for-profit association called Alpha-1 PLUS to advocate for the disease and challenge this discrimination. For me it is unfair and unjust that people with the same genetic condition and similar lung function do not have the same right to get the best treatment available in their country.

In Europe, healthcare decision making is a national policy issue and not a European affair: in every country the diagnosis and treatment of “Alpha-1 conditions” are different. In some countries, augmentation therapy is reimbursed by the national health insurance, in others reimbursement is limited to a very small number of people and in some countries, it is not available at all. Some patients move to another country to get access to therapy. For me to create awareness is the most important activity: to speak about AATD on social media, to inform doctors and to organise events with politicians and other stakeholders.

Final thoughts

These patient stories clearly highlight the significant burden that people with AATD face on many different levels. These include the significant effort and time necessary to maintain a healthy lifestyle through dedicated and targeted exercise and nutritional eating plans. In addition, the emotional and psychological burden of living with this condition is immense for patients and their families. This is exacerbated by significant geographic differences in the availability of specific treatment options. Progress in systematic genetic testing for AATD to accelerate diagnosis once first signs and symptoms develop, equal patient access to all therapeutic options across Europe and more focussed research into this rare disease and



Figure 3 Frank Willersinn.

the development of effective disease-modifying therapies would help to reduce the disease burden and address the continued unmet need faced by individuals with AATD.

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Conflict of interest

M. Wilkens as chairman of the patient organisation Alpha1 Deutschland e.V. does not receive any donations, but the organisation receives money from public funds as well as from the pharmaceutical industry. For example, grants as well as travelling costs. K. O'Hara reports non-financial support from ELF/ERS, non-financial support from Mereo BioPharma Group PLC, the Alpha-1 UK Support Group has received grants from CSL Behring and also receives donations from individuals/companies as a result of fundraising activities, personal fees and non-financial support from NICE, non-financial support from Alpha-1 Global, outside the submitted work. J. Boyd is an employee of the European Lung Foundation. J. Denning is an employee of the European Lung Foundation.

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1. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003; 168: 818-900.