CASE REPORT

Hidden burden of osteoporosis in alpha-1 antitrypsin deficiency

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SUMMARY

This is a reminder of a rare cause of osteoporosis that remains widely underdiagnosed and lacks specific evidence on its optimal management. We bring a case report of a patient presenting with erectile dysfunction and high testosterone level but also elevated sex-hormone binding globulin hence low free androgen index as well as evidence of organ specific hypogonadal side effects such as osteoporosis. A unifying diagnosis of alpha-1 antitrypsin deficiency (AATD) brought together his coexistent mild chronic obstructive pulmonary disease as well as a new finding of previously unrecognised liver disease. This case highlights the uncertainties over the mechanism of osteoporosis in AATD as well as the controversies over best way to manage it. The efficacy of testosterone replacement in managing osteoporosis in the context of AATD remains untested. National registries for AATD would be best placed at gathering further evidence in this area.

question the additional contribution from other factors such as under-recognised functional hypogonadism.

A prospective study in patients with COPD on the Danish national registry referred for long-term oxygen therapy (LTOT) found that osteoporosis was more frequently found (28.5% vs 20.4%, $p=0.002$) in patients with AATD versus COPD without AATD, despite younger age and less cardiovascular and diabetes comorbidities.¹² None of the patients with AATD received augmentation therapy in this study.

Another study found osteoporosis in 42.1% of 19 patients with AATD with a PiZZ genotype, the majority of which were newly diagnosed in previously unsuspected patients (seven out of eight patients) who did not receive maintenance oral steroids. The bone density was significantly lower at both hip and spine than matched controls.¹³

This suggests a potential underdiagnosed burden of osteoporotic bone disease in patients with AATD which is not being treated.

There remains controversy over the mechanism of osteoporosis in AATD as well as lack of guidance on its most appropriate management, which is hampered by the rarity of diagnosed cases; hence, further coordinated research is required to elucidate this area.

We present the case of a patient identified with AATD following an unusual presentation with erectile dysfunction and high testosterone level but also elevated sex-hormone binding globulin (SHBG) leading to low free androgen index hence hypogonadal symptoms. Findings of osteoporosis on bone density scan were in accordance with hypogonadal side effects on the bone. The confirmation of underlying AATD matched with his coexistent mild COPD. The pattern of elevated testosterone and SHBG is very well described in previous AATD studies, even in the absence of documented liver disease.¹⁴ Handelsman *et al* identified very similar findings of a statistically significant increase in total testosterone but reduction in percentage of free testosterone compared with healthy controls, illustrative of underlying elevated SHBG status in eight patients with AATD with severe COPD but no reported liver disease. Given the rarity of the disease, further studies would be needed to confirm that these findings are not due to chance. National registries for AATD would be best placed at gathering further evidence in this area.

BACKGROUND

November is Alpha-1 Awareness Month.

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder estimated to affect 1 in 1500 to 3500 Caucasians, while uncommonly reported in Asians.¹ Its incidence is widely underestimated, with studies in the chronic obstructive airways disease (COPD) population showing an incidence of 1%–2%.^{2,3} While the disorder is under-recognised,⁴ the delay from first presentation of symptoms to diagnosis is typically long, exceeding the shortest reported span of 5.6 years.^{5,6}

The conditions most commonly associated with AATD are emphysema and bronchiectasis with early onset by fourth or fifth decade and liver disease such as chronic hepatitis and cirrhosis. Other well-recognised but rare associations are panniculitis and also uncommonly systemic vasculitis,⁷ glomerulonephritis,⁸ vascular disease⁹ and inflammatory bowel disease.¹⁰ Evidence for these associations are widely available, most reliably from national registry details such as the UK national centres for patients with AATD.¹¹

Osteoporosis is widely described in patients with AATD, unsurprisingly given the effect of chronic respiratory conditions, chronic undernutrition and exposure to exogenous steroids. However, studies on patients with AATD with mild COPD and no prior exposure to steroids also document the presence of osteoporosis, even where chronic liver disease is not documented. This brings into

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Table 1 Initial blood investigations

Investigation	Normal range	Units	Test 1	Test 2
LH	1.7–8.6	U/L	6.6	13.0
FSH	1.5–12.4	U/L	15.8	19.5
Testosterone	6.7–25.7	nmol/L	37.1	>52
Testosterone by mass spectrometry	9–27	nmol/L	32.6	
SHBG	15–55	nmol/L	217	209
Albumin	35–50	g/L	36	34
Protein	60–80	g/L		72

LH Luteinising hormone, FSH Follicle Stimulating Hormone, SHBG, sex-hormone binding globulin.

CASE PRESENTATION

A 61-year-old Caucasian presented to his general practitioner with symptoms of fatigue and erectile dysfunction. He reported no abnormal sweating. He was found to have elevated testosterone and gonadotrophins and was referred to the Endocrine Clinic for further management.

He had background of mild COPD diagnosed 7 years previously as well as stable diverticular disease. His current medication included only Tiotropium inhaler which he used occasionally during exacerbation of symptoms, and he has never had any exposure to oral or inhaled steroid treatment previously. He had no relevant alcohol history. He has been a cigar smoker for approximately 35 years but stopped 6 years prior to his presentation. He had no history of weight loss.

Clinically, he was documented to have spider naevi but no other stigmata for chronic liver disease. He had normal secondary sexual characteristics.

INVESTIGATIONS

Biochemistry investigations (tables 1 and 2) showed elevated SHBG indicative of much lower percentage free testosterone level and decreased free androgen index, in keeping with his presenting hypogonadal symptoms. His free androgen index was low at 17 (normal 30–170) and the calculated free testosterone (Vermeulen formula)¹⁵ was 0.184 nmol/L (0.494%).

Liver function tests showed mildly increased transaminases and gamma-glutamyltransferase (gamma-GT) up to 1.5 times the upper limit of normal (alanine aminotransferase 50 IU/L, normal <42 and gamma-GT 91 IU/L, normal <60 IU/L), but satisfactory synthetic liver function (albumin 34 g/L, normal 35–50 g/L, clotting normal) and normal detoxifying liver function (bilirubin normal).

Liver ultrasound showed diffuse heterogeneous echotexture in keeping with hepatic steatosis as well as mildly irregular liver surface; however, a CT scan of the liver showed no features of cirrhosis, and transient elastography (Fibroscan) showed a score of 8.5 kPa, which corresponds to fibrotic stage F1 (mild fibrosis) for liver disease. The patient did not consent so far to a diagnostic liver biopsy, while he remains under close hepatology surveillance.

Lung function tests were consistent with GOLD stage 1 group A for the severity of COPD: forced expiratory volume in one second (FEV1) 2.68 L (99.4%), forced vital capacity 4.74 L (149.2%), FEV1/VCmax 56.37%, total diffusing capacity of the lung 8.1 L (96.3%), transfer coefficient 1.12 L (76.2%).

Further investigations with a bone density scan confirmed underlying osteoporosis: T score –2.8 at left neck of femur and –2.1 at left hip and –1.8 at spine.

Table 2 Laboratory workup investigating alternative causes for osteoporosis

Investigation	Normal range	Units	Result
cCa	2.20–2.60	nmol/L	2.37
PTH	1.6–6.9	pmol/l	3.4
Magnesium	0.70–1.00	mmol/L	0.80
Phosphate	0.80–1.50	mmol/L	0.86
TSH	0.27–4.20	mU/L	0.49
FT4	11.0–22.0	pmol/L	15.8
Serum electrophoresis	Normal gamma fraction but decreased alpha band		
Alpha-1 antitrypsin	1.1–2.1	g/L	0.030
ALT	<42	IU/L	50
ALKP	30–130	U/L	84
Gamma-GT	<60	IU/L	91
Bilirubin	<21	µmol/L	9
IGA	0.70–4.00	g/L	6.63
HCG	<4	IU/L	<2
AFP	<7	ng/mL	6
FBC			Normal
Prothrombin time	9–14	s	13
INR	0.8–1.2		1.1
Urea and electrolytes			Normal
Coeliac screen			Negative
Urinary Bence Jones proteins			Negative
A1AT genotype	Homozygous for the Z variant (c.1096G>a; p.Glu288Val) in the AAT SERPINA1 gene.		

cCa Corrected Calcium, PTH Parathyroid Hormone, TSH Thyroid Stimulating Hormone, FT4 Free thyroxine, ALT Alanine aminotransferase, ALKP Alkaline Phosphatase, Gamma-GT gamma-glutamyltransferase, IGA Immunoglobulin A, HCG Human Chorionic Gonadotropin Hormone, AFP Alpha fetoprotein, FBC Full Blood Count, INR International normalised ratio, A1AT Alpha 1 antitrypsin.

Following identification of low alpha-1 antitrypsin level and reduced alpha 1 band on serum electrophoresis, genetic testing confirmed a PiZZ genotype diagnostic for homozygous A1AT.

DIFFERENTIAL DIAGNOSIS

Screening for alternative causes of osteoporosis revealed no other potential aetiology: normal thyroid function, calcium, phosphate, magnesium, parathyroid hormone, negative coeliac screen.

TREATMENT

He was given calcium and vitamin D supplements alongside a trial of parenteral testosterone, consisting of Nebido 1 g every 12 weeks, prompted by patient's desire to address his erectile dysfunction symptoms.

OUTCOME AND FOLLOW-UP

The impact on bone density was assessed with an interval bone density scan at 2 years.

We postulated on the challenges of testosterone replacement in the presence of elevated SHBG, since it was expected that binding to SHBG may limit the efficiency of boosting free testosterone levels. The efficiency of this approach was not previously reported and the patient was fully counselled on its uncertainties. We found little if any improvement in SHBG and gonadotrophin levels at subsequent follow-up, but were limited in titrating the doses given that our subject developed mild acne while on parenteral treatment.

A follow-up bone density scan at 2 years interval showed a decline in bone density particularly at the lumbar region, mandating a revision of his treatment approach. He was subsequently switched to parenteral Zoledronic acid.

DISCUSSION

We present a rare case of first diagnosis of AATD following atypical presentation with hypogonadal symptoms. Hypogonadism is not classically described in this condition; however, abnormalities of the gonadal axis hormone pattern have previously been well documented,¹⁴ including elevated total testosterone and SHBG but lower free testosterone as well as higher gonadotrophin levels compared with controls. No abnormalities of libido or secondary sexual characteristics were previously described. Studies of gonadal function in patients with AATD are, however, scarce; hence we explore the possibility of hypogonadism being under-reported.

Fatigue is a common symptom reported in AATD. A study of patients with AATD found severely impaired quality of life compared with patients with COPD without known AATD and also patients with AATD were more likely to report difficulties in personal relationships.¹⁶ Since this is a common unrecognised symptom of hypogonadism, it brings into question whether abnormalities of gonadal axis may underpin such reported abnormalities.

Decreased skeletal muscular mass is another sign correlated to hypogonadism, and a study reporting such findings compared with controls found significantly higher early morning total testosterone levels compared with matched controls in patients with AATD, with or without osteoporosis.¹³ No SHBG or free testosterone status was ascertained, however, by the study, given that measurements of total testosterone alone can be misleading, but findings match reports from other small studies.

Elevated total testosterone level with reduced percentage free testosterone level, indicative of high SHBG status, was reported in patients with AATD with severe COPD but minimal or no evidence of hepatic impairment (elevations in liver enzymes <1.5 ULN, normal liver scan).¹⁴ Plasma total testosterone was significantly higher in the subgroup of patients with mild abnormalities in liver enzymes and it was speculated to be linked to elevated SHBG and represent a marker of early subclinical liver disease in AATD.

We believe that the hypogonadal symptoms in our subject relate to a compensated hypogonadal state with elevated SHBG leading to decreased bioavailability of testosterone and rising gonadotrophin levels. The elevated SHBG is explained by his early liver derangement, and while our subject did not proceed to liver biopsy, it is highly likely that he is affected by AATD-related hepatitis.

We ascertain that liver disease in AATD is notoriously difficult to detect and typically silent until advanced stages hence diagnosed late. Efforts to improve detection have recently concentrated on the value of transient elastography (Fibroscan) in detecting early liver involvement. The Fibroscan scoring is, however, not currently validated in AATD. A clinical trial is currently in progress to assess its sensitivity and expected to report evidence by 2021.¹⁷ Preliminary retrospective data are supportive for the clinical usefulness of Fibroscan in early diagnosis of liver involvement in patients with AATD, allowing for targeting of modifiable risk factors in preventing disease progression.¹⁸

Elevated SHBG is well documented in a variety of other liver disorders such as alcoholic liver disease, haemochromatosis,

Table 3 Factors determining SHBG levels

Decreased SHBG	Androgens Progesterone Polycystic ovarian syndrome Congenital Adrenal Hyperplasia Obesity Insulin resistance Metabolic syndrome Type 2 diabetes mellitus Non-alcoholic fatty liver disease Acromegaly
Increased SHBG	Oestrogen Pregnancy Weight loss Alcoholic cirrhosis Haemochromatosis Hyperthyroidism Individual genetic polymorphism

SHBG, sex-hormone binding globulin.

while low SHBG is documented in non-alcoholic fatty liver disease.¹⁹

Of note, studies of endocrine status in men following liver transplantation for liver cirrhosis document an improvement in SHBG status with significant decrease in its level.²⁰

The underlying pathophysiology for SHBG changes in liver disease remains subject to speculation. Well recognised factors influencing SHBG levels are nutritional status, adipose tissue mass, androgen levels, growth hormone, genetic polymorphism and differences in SHBG glycosylation with genetic variants being degraded more slowly (table 3). At genetic level, the SHBG gene promoter sequence dictates the gene transcription activity and resulting SHBG levels in the blood.²¹

Our subject has a typical pattern of elevated SHBG and testosterone level observed in patients with AATD; hence, SHBG gene polymorphism causing elevated SHBG is less likely to be the case. There are no similarities between the genes controlling SHBG (a single gene on the short arm of chromosome 17) and the AATD gene SERPINA1 (located on the long arm of chromosome 14).²²

Our case illustrates the challenges of testosterone replacement in hypogonadal males with elevated levels of SHBG, not least in respect to its monitoring and titration against the usual biochemical markers. While there is observational evidence of improvement in metabolic syndrome and non-alcoholic fatty liver steatosis in hypogonadal men treated with parenteral testosterone,²³ such evidence has not been systematically explored in AATD. Testosterone may not be the optimal modality of tackling

Learning points

- ▶ Alpha-1 antitrypsin deficiency (AATD) is under-recognised and delays are common in its diagnosis from initial presentation.
- ▶ Osteoporosis is under-reported in AATD and likely to be multifactorial; however, its specific pathogenic mechanism is not definitely established.
- ▶ There is a need to explore the extent of unrecognised hypogonadism that could explain the higher incidence of osteoporosis in patients with AATD compared with chronic obstructive pulmonary disease without AATD.
- ▶ While testosterone replacement can bring multiple metabolic benefits, it has, however, disputable efficacy as treatment for osteoporosis in the context of the rare presentation of hypogonadism in AATD-related osteoporosis.

pre-existent osteoporosis in males with AATD with confirmed hypogonadism and comes with additional challenges in monitoring and titration. We promote an increased awareness of AATD in the medical community as well as collaboration with the national registries for AATD which are best placed to gather evidence for its optimal management.

Contributors All authors have had major contributions to the case presented, bringing a unique perspective from their own specialty field. The case report was reviewed and approved by all authors. EF (previously Bejinariu) was involved in the writing of the manuscript, clinical review of the patient described in the case report in the Endocrinology Clinic and soliciting support from the associated specialties in the expert review of the patient. IS was involved in the revision of the manuscript and was in charge of the clinical care of the patient described in the case report in the Respiratory Medicine Clinic. He also facilitated the coordination of Genetics investigations. PK was involved in the revision of the manuscript and was in charge of the clinical care of the patient described in the case report in the Hepatology Clinic. RB was involved in the revision of the manuscript and was in charge of the clinical care of the patient described in the case report in the Endocrinology Clinic.

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