

Hereditary angioedema may be associated with the development of fatty liver



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Clinical Implications

- Fatty liver may be quite common in patients with hereditary angioedema (HAE). Patients with HAE should be screened for fatty liver as well as other conditions that may be associated with it.

TO THE EDITOR:

Hereditary angioedema (HAE) is a rare but potentially fatal disease. It is characterized by episodic isolated angioedema. HAE affects an estimated 1:10,000 to 1:50,000 patients.¹ The clinical features of HAE might include swellings of the skin, upper airway, or gastrointestinal tract.²

Danazol is one of the prophylactic treatments for HAE. It may work by improving the level of C1 inhibitor protein in patients with HAE, thereby reducing attacks associated with the disease.³ However, the use of Danazol is associated with liver side effects.⁴ Liver parameters including liver enzymes as well as liver ultrasound (US) should be done at baseline before starting Danazol and periodically during use to monitor its side effects.

We observed a high frequency of nonalcoholic fatty liver disease (NAFLD) in patients with HAE even before starting Danazol, but the prevalence remains unknown. The pathogenesis of NAFLD has not been fully elucidated. Multiple pathways

may be involved in the complex pathogenesis of NAFLD.⁵ Patients with NAFLD may be pregnant or have obesity, hyperlipidemia, diabetes, metabolic syndrome, malnutrition, or a sedentary lifestyle. Certain other conditions such as polycystic ovary syndrome, hypothyroidism, obstructive sleep apnea, and hypopituitarism have also been associated with NAFLD.⁶ NAFLD is more commonly observed in the elderly and in people with a higher body mass index (BMI).⁷

We sought to determine the prevalence of NAFLD as diagnosed by US in patients with HAE presenting to our hospital for the last 15 years, before starting Danazol. This study was approved by the hospital's research advisory committee (RAC # 2141 147) and assigned publication no. 2180421.

A total of 48 patients were identified. Abdominal US results done at baseline were available for 42 of those patients. Two of those 42 patients were further excluded as they had abnormal liver function tests at baseline. There was no history of alcohol consumption in any of the study patients. The age of the patients ranged from 6 to 79 years with a mean of 29.2 years and a median of 31 years; standard deviation was ± 17.8 . A total of 60% of the patients were females. BMI ranged between 14.3 and 48.5 with a mean of 25.7 and a median of 29.1; standard deviation was ± 5.7 .

A total of 82.5% of the patients had HAE type I, whereas 17.5% had HAE type II. Lipid profile revealed that only 17.5% had high cholesterol and triglyceride levels, and low density lipoprotein (LDL) was high in 32.5% of the patients. The percentage of people with HAE who had hypertension and diabetes was 28.88% and 5.88 % respectively (Table I).

The prevalence of fatty liver by US in patients with HAE who presented to our hospital was 47.5%. Of this, 84.2% had HAE type I and 15.8% had HAE type II. The majority of cases of NAFLD (26.3% each) were in patients either less than 18 years old or between 35 and 44 years old; 10.53% were between

TABLE I. Demographics of HAE patients with NAFLD

Total no. of patients	40
Age (y)	Mean: 29.2 (6-79); median: 31
Sex	M: 16 (40%) F: 24 (60%)
BMI	Mean 25.7 (14.3-48.5); median: 29.1
Diabetes rate	5.88%
Hypertension rate	28.88%
HAE type	I: 82.5% II: 17.5%
Total cholesterol (normal: less than 6.2 mmol/L)	Normal: 33 (82.5%) High: 7 (17.5%)
LDL (normal: less than 4.1 mmol/L)	Normal: 27 (67.5%) High: 13 (32.5%)
HDL (normal: more than 1.04 mmol/L)	Normal: 28 (70%) High: 12 (30%)
Triglycerides (normal: less than 2.26 mmol/L)	Normal: 33 (82.5%) High: 7 (17.5%)

BMI, Body mass index; HAE, hereditary angioedema; HDL, high density lipoprotein; LDL, low density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

TABLE II. Demographics of HAE patients with NAFLD

Percentage of HAE patients with NAFLD	47.5%
HAE type	I: 84.2%
	II: 15.8%
Age distribution of NAFLD	Less than 18: 26.3%
	18-24: 10.53%
	35-44: 26.3%
Dyslipidemia	26.3%
Diabetes	5.26%

HAE, Hereditary angioedema; NAFLD, nonalcoholic fatty liver disease.

18 and 24 years old. A total of 26.3% of patients with HAE who had NAFLD also had dyslipidemia, and 5.26% of the patients with NAFLD also had diabetes (see Table II).

In a recent article, the percentage of people in the Saudi general population with hypertension and diabetes was found to be 29.75% and 32%, respectively.⁸ Standard ultrasonography criteria (*the so-called bright liver*) were used for the diagnosis of NAFLD.⁹ There is an extremely high prevalence NAFLD in our patients with HAE (47.5%) compared with approximately 16.6% in a recent study of the Saudi population where there was no reported case of HAE in that cohort.¹⁰ This is despite the fact that our patients were younger and had a lower BMI. The mean age in the reference population was 44.7 with the standard deviation of ± 11.5 . Their BMI was 34.5 with the standard deviation of ± 8.1 . A *t*-test for the difference in 2 means was used to compare age and BMI. Both BMI ($P < .01$) and age ($P < .01$) were statistically different between the populations. Our patients were on average 15 years younger and with BMI lower by 6 kg/m². A *z*-score test for the difference in 2 proportions was used to compare gender. We found that gender was not statistically different across the 2 populations ($P > .10$).¹⁰

Recently, it has been argued that HAE should be viewed as a metabolic liver disease.⁴ Whether HAE itself contributes to the pathogenesis of NAFLD in these patients is unknown.

Aggressive lifestyle modifications (diet and exercise) in patients with HAE before starting Danazol may help reduce these side effects of Danazol in patients with HAE. Furthermore, physicians should be cautious in starting medicines like tetracycline or amiodarone in patients with HAE, as it might make their NAFLD worse. Patients should also be screened for other conditions such as obesity, hyperlipidemia, diabetes, metabolic syndrome, malnutrition, or a sedentary lifestyle. Patients should also be screened for polycystic ovary syndrome, hypothyroidism, obstructive sleep apnea, and hypopituitarism, with known association with NAFLD where appropriate. To our knowledge, this is the first study evaluating the prevalence of

fatty liver in patients with HAE at baseline, before starting Danazol.

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