

Madelung's disease and acute alcoholic hepatitis: case report and review of literature

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Abstract. – Madelung's disease is a rare condition characterized by symmetric growth of fatty tumors (lipomas) around the neck, shoulders, upper arms, and trunk. It often affects men with a history of alcohol abuse. Here we report a review of the literature about this disease together with the description of a patient affected by Madelung's disease and acute alcoholic hepatitis.

Key Words:

Madelung's disease, Alcohol use disorder, Acute alcoholic hepatitis.

Introduction

Madelung's disease is a rare disorder of unknown etiology; the name comes from the German surgeon Otto Madelung who in 1888 reported the first series of 33 patients with fat necks and named this condition "Madelung's collar"¹. It is characterized by painless, benign, and symmetric lipomatosis, a subcutaneous accumulation of non-encapsulated adipose tissue.

Two types of disease can be observed, depending on the distribution of lipomatosis²:

Type I: is characterized by the accumulation of fat deposits around the neck, arms, mediastinum, and upper body ("bull's neck" appearance) and it occurs more frequently in males. In other parts of the body, the fat is equally distributed;

Type II: is similar to gynoid obesity with accumulation of fat in the upper back, deltoid area, hips (such as simple obesity), and thighs and it affects males and females^{3,4}.

In a recent classification⁵, three types of Madelung's disease have been identified:

Type I, with neck distribution of lipomatosis;
Type II, with pseudoathletic appearance;
Type III, with gynecoid distribution of lipomatosis.

However, in some patients more than one type could be present. Patients affected by Madelung's disease are between 30 and 60 years old, with a high prevalence among males (M:F ratio 15-30:1) in Mediterranean countries^{6,7}. The etiology is unknown, but different pathophysiological mechanisms have been hypothesized. One of these is the hypertrophy of brown adipose tissue (BAT) due to impaired adrenergic lipolysis induced by catecholamine disturbance⁸, or modification in the beta-adrenergic receptors⁹. This hypothesis is based on the observation that the areas affected by Madelung's disease are the main ones of BAT¹⁰. Moreover, uncoupling protein 1 (UCP1), specific for BAT, has been detected in biopsies taken from lipomas in patients suffering from the Madelung's disease⁷. In a recent case report, Moonen et al¹¹ showed the presence of inactive BAT in a patients with Madelung's disease, using an individualized cooling procedure and 18F-FDG-Positron Emis-

sion Tomography/Computed Tomography (PET/CT)⁷, suggesting that alterations in adrenergic pathways and BAT metabolism play a central role in the proliferation of adipocytes leading to the formation of lipomas.

Specific point mutations within mitochondrial DNA (mtDNA) may also be involved; Perera et al¹² showed the presence of a rare MTTK gene c.8344A>G variant in a Canadian family with multiple family members affected by Madelung's disease.

Moreover, an association between Madelung's disease and diabetes mellitus, hyperuricemia, hypothyroidism, liver disease, peripheral neuropathy, and alcohol use disorder has been described¹³. The association with chronic alcohol abuse has been found in 60-90% of the reported cases^{14,15}. It seems that alcohol directly affects mitochondrial metabolism and causes premature oxidative aging of the mtDNA¹⁶, decreasing the beta-adrenergic receptors⁵.

Here we describe a case of a patient affected by Madelung's disease and acute alcoholic hepatitis.

Case Report

A 47-year-old man was admitted to the Internal Medicine and Hepatogastroenterology Department for the onset of jaundice. His history was significant for heavy alcohol consumption (about 16 drinks/day until 2 days before hospitalization). His medications included propranolol and pantoprazole. At admission, the patient was alert and afebrile. Vital signs were normal. At physical examination jaundice, cutaneous spider naevi, hepatomegaly, splenomegaly, ascites, and gynecomastia



Figure 1. This figure shows patients with swelling of the neck and acute alcoholic hepatitis. It also shows the presence of jaundice, cutaneous spider naevi, and facial erythrosis.



Figure 2. This figure shows right side profile of patients with Madelung's disease and acute alcoholic hepatitis.

were noted. A painless, soft swelling of the neck with no signs of inflammation was also detected (Figures 1 and 2). The remaining physical examination was unremarkable. Serum test showed the picture of severe liver failure (Table I). Tests for viral, autoimmune, and genetic etiologies of liver disease were negative. Abdominal ultrasounds scan showed signs of advanced liver disease and ascites. Gastroscopy showed grade 3 esophageal varices. The Maddrey Discriminant Function score was 120, thus prednisolone (40 mg/day) and N-acetylcysteine were administered with a partial improvement of liver function. Ultrasound scan of the neck showed soft echogenic encapsulated masses located in the subcutaneous tissue, with no acoustic shadowing and no color Doppler flow (Figure 3). No size and structure alterations of salivary and thyroid glands, nor lymph nodes enlargement were present. Thyroid and renal function were normal. The patient's lipid profile was unremarkable. A CT scan of the neck and thorax showed an abnormal growth of adipose tissue in submandibular region and in the area of the neck, especially in the anterior portion, described as diffuse and symmetric lipomatosis.

A clinical diagnosis of Madelung's disease was made. Since our patient was asymptomatic for dyspnea and dysphagia no surgical treatment was proposed. He was discharged and he was referred to an Alcohol Addiction Unit and to Transplantation Center, respectively for the treatment of Alcohol Use Disorder and to evaluate eligibility for liver transplantation. During the follow-up, the patient relapsed in alcohol

Table I. Results of blood tests at the hospitalization and after one week of treatment.

Variable	At admission	After 1 week	Reference range
Erythrocyte count (per mm ³)	2,980 × 10 ³	3,090 × 10 ³	4,300-6,100 × 10 ³
Hemoglobin (g/dl)	11.2	11.3	13.0-17.0
Mean corpuscular volume (fl)	108.6	112.0	81.0-99.0
White-cell count (per mm ³)	2,980	12,310	4,100-9,800
Platelet count (per mm ³)	51,000	48,000	140,000-450,000
Glucose	124	117	65-110
Creatinine (mg/dl)	1.08	1.01	0.67-1.17
Sodium (mmol/l)	137	133	135-145
Potassium (mmol/l)	3.1	4.9	3.5-5.0
Bilirubin (mg/dl)			
Total	26.10	19.9	0.3-1.2
Direct	19.4	15.4	< 0.3
Alkaline phosphatase (U/L)	171	168	40-129
Alanine aminotransferase (U/L)	58	52	7-45
Aspartate aminotransferase (U/L)	177	123	7-45
Triglycerides (mg/dl)	148	146	50-150
Cholesterol (mg/dl)	158	160	120-200
Albumin (g/dl)	2.3	2.5	3.4-4.8
Activated partial-thromboplastin time (sec)	65.10	54.40	20.00-39.00
Prothrombin time (sec)	35.80	29.00	10.00-12.00
International normalized ratio	3.10	2.58	0.80-1.20

and decided to interrupt the treatment; for this reason, it was not possible to propose the patient for a transplant study. The mass did not seem to have reduced significantly in size.

Discussion

Madelung's disease has been highly associated with alcohol use disorder (60-90% of the reported case)^{14,17} but it has also been associated with other diseases such as diabetes mellitus, hyperuricemia, hypothyroidism, liver disease,

and peripheral neuropathy¹⁴. In our patient, alcohol abuse and alcohol liver disease were the only factors associated with Madelung's disease and no other cofactor was present.

Brea-Garcia et al¹⁴ showed that 95.5% of a series of 22 patients with Madelung's disease reported high alcohol intake. Moreover, in a retrospective analysis¹⁸ of 10 patients affected by the disease who underwent surgical interventions, alcohol abuse with a consumption of more than 450 g of ethanol per day was evident. In a series of 17 Madelung's cases studied by Semenenou et al¹⁹, all patients were alcoholic.

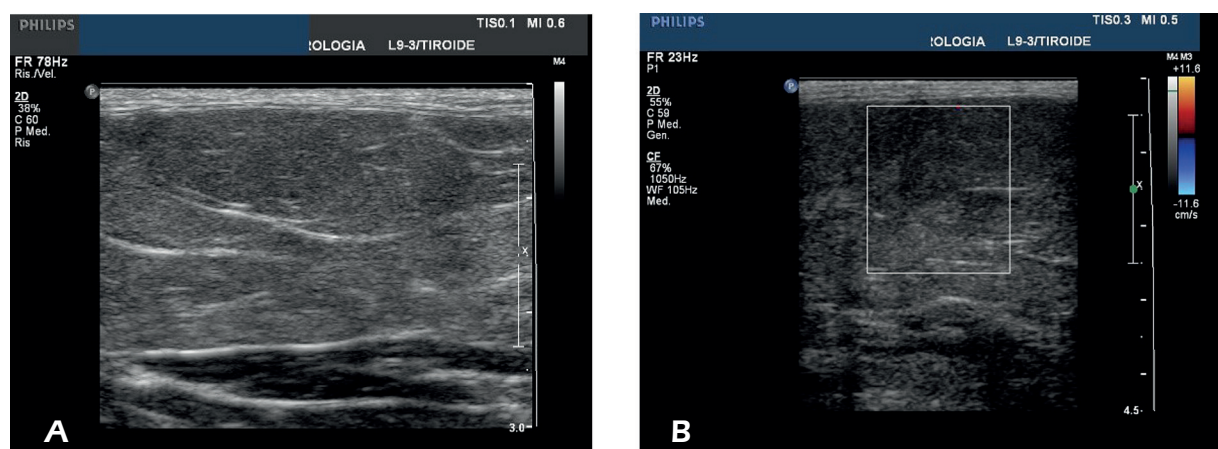


Figure 3. A, B, These figures show echogenic encapsulated masses located in the subcutaneous tissue, with no acoustic shadowing and no color Doppler flow.

Ethanol abuse is known to promote lipogenesis and decrease lipolysis leading to uncontrolled accumulation of adipose tissue in various parts of the body^{4,20}.

Indeed, alcohol could affect mitochondria functions causing premature oxidative aging of mtDNA and disrupting adrenergic lipolysis¹⁶.

Differential diagnosis includes solitary lipoma, encapsulated lipoma, familial multiple lipomatosis, liposarcoma, Cushing syndrome, angiolipomatosis, neurofibromatosis, and lymphoma²¹. For these reasons, the clinical examination must be supported by a CT scan showing the accumulation of non-encapsulated fat in the subcutaneous tissue or within spaces between muscles²². The imaging exam is useful for the evaluation of the extension of adipose tissue deposition, tracheal compression, presence of blood vessels within the adipose mass, and malignant transformation (however rare)¹⁷. There is no possible pharmacological treatment, except for the elimination of pathogenic noxa, in Madelung's disease. Dietary restriction has not been reported to influence lipomatosis, even if alcohol abstinence could delay the progression of the disease¹⁶. Although clinical and behavioral measures could not reverse or ameliorate the medical disease, alcohol withdrawal and weight loss are recommended¹⁸.

Extensive lipectomy remains the standard treatment for Madelung's disease. Although benign in nature, sometimes the fatty masses can reach very large sizes leading to dyspnea, dysphagia, fatigue, reduced neck movement ability, and psychological stress. In these cases, the treatment was represented by surgical removal or liposuction⁸. Pinto et al⁵, in a review of 59 surgical cases with Madelung's disease, showed a tendency toward a relapse of lipomatosis using liposuction techniques when compared to lipectomy (20% vs. 14.1%). They suggested that lipectomy provides better aesthetic and functional results, compared to liposuction.

Conclusions

Physicians who identify patients with suspected Madelung's disease should investigate their drinking history/alcohol addiction. If positive, patients should be encouraged to stop drinking, since only total alcohol abstinence could prevent the rise of lipomatosis size and recurrence after surgical treatment. They should also be referred to an Alcohol Addic-

tion Unit to start a pharmacological treatment for Alcohol Use Disorder²³. Furthermore, due to the possible presence of alcohol-related disease^{24,25}, these subjects should be screened for other alcohol-related diseases such as liver and cardiovascular, respectively, with abdominal and cardiac ultrasonography^{26,27}.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) MADELUNG OW. Ueber den Fetthals. *Archi Fuer Klinische Chirurgie* 1888; 37: 106-130.
- 2) ENZI G, Busetto L, Ceschin E, COIN A, DIGITO M, PIGOZZO S. Multiple symmetric lipomatosis: clinical aspects and outcome in a long-term longitudinal study. *Int J Obes Relat Metab Disord* 2002; 26: 253-261.
- 3) GAO H, XIN ZY, YIN X, ZHANG Y, JIN QL, WEN XY. Madelung disease: a case report. *Medicine (Baltimore)* 2019; 98: e14116.
- 4) SZEWC M, SITARZ R, MOROZ N, MACIEJEWSKI R, WIERZBIK R. Madelung's disease--progressive, excessive, and symmetrical deposition of adipose tissue in the subcutaneous layer: case report and literature review. *Diabetes Metab Syndr Obes* 2018; 11: 819-825.
- 5) PINTO CI, CARVALHO PJ, CORREIA MM. Madelung's disease: revision of 59 surgical cases. *Aesthetic Plast Surg* 2017; 41: 359-368.
- 9) KO MJ, CHIU HC. Madelung's disease and alcoholic liver disorder. *Hepatology* 2010; 51: 1466-1467.
- 6) MAXIMIANO LF, GASPAR MT, NAKAHIRA ES. Madelung disease (multiple symmetric lipomatosis). *Autops Case Rep* 2018; 8: e2018030.
- 7) WOLLINA U, HEINIG B. Madelung's disease – case series and treatment by tumescent liposuction or lipectomy. *Open Access Maced J Med Sci* 2017; 19; 5: 427-431.
- 9) ENZI G, INELMEN E, BARITUSSIO A, DORIGO P, PROSDOCIMI M, MAZZOLENI F. Multiple symmetric lipomatosis--a defect in adrenergic-stimulated lipolysis. *J Clin Invest* 1977; 60: 1221-1229.
- 10) ALAMEDA YA, TORRES L, PEREZ-MITCHELL C, RIERA A. Madelung disease: a clinical diagnosis. *Otolaryngol Head Neck Surg* 2009; 141: 418-419
- 11) MOONEN MPB, NASCIMENTO EBM, VAN KROONENBURGH MJPG, BRANDJES D, VAN MARKEN LICHTENBELT WD. Absence of 18 F-fluorodeoxyglucose uptake using positron emission tomography/computed tomography in madelung's disease: a case report. *Clin Obes* 2019 Feb 27; e12302. doi: 10.1111/cob.12302. [Epub ahead of print].

- 12) PERERA U, KENNEDY BA, HEGELE RA. Multiple symmetric lipomatosis (Madelung disease) in a large canadian family with the mitochondrial MTTK c.8344A>G variant. *J Investig Med High Impact Case Rep* 2018; 6: 2324709618802867.
- 13) MEVIO E, SBROCCA M, MULLACE M, VIGLIONE S, MEVIO N. Multiple symmetric lipomatosis: a review of 3 cases. *Case Rep Otolaryngol* 2012; 2012: 910526.
- 14) BREA-GARCÍA B, CAMESELLE-TEJEIRO J, COUTO-GONZÁLEZ I, TABOADA-SUÁREZ A, GONZÁLEZ-ÁLVAREZ E. Madelung's disease: comorbidities, fatty mass distribution, and response to treatment of 22 patients. *Aesthetic Plast Surg* 2013; 37: 409-416.
- 15) HIROSE A, OKADA Y, MORITA E, TANAKA Y. Benign symmetric lipomatosis associated with alcoholism. *Intern Med* 2006; 45: 1001-1005.
- 16) GONZÁLEZ-GARCÍA R, RODRÍGUEZ-CAMPO FJ, SASTRE-PÉREZ J, MUÑOZ-GUERRA MF. Benign symmetric lipomatosis (Madelung's disease): case reports and current management. *Aesthetic Plast Surg* 2004; 28: 108-112; discussion 113.
- 17) TADISINA KK, MLYNEK KS, HWANG LK, RIAZI H, PAPAY FA, ZINS JE. Syndromic lipomatosis of the head and neck: a review of the literature. *Aesthetic Plast Surg* 2015; 39: 440-448.
- 18) GAO Y, HU J-L, ZHANG X-X, ZHANG M-S, LU Y. Madelung's disease: is insobriety the chief cause? *Aesthetic Plast Surg* 2017; 41: 1208-1216.
- 19) SEMENOU D, COEUGNIET E, SEGARD M, MARTINOT-DUQUENNOY V, DELAPORTE E. [Launois-Bensaude's disease: report of 17 cases]. *Ann Chir Plast Esthet* 2008; 53: 399-407.
- 29) LÜSCHER NJ, PREIN J, SPIESSL B. Lipomatosis of the neck (Madelung's neck). *Ann Plast Surg* 1986; 16: 502-508.
- 21) ARDELEANU V, CHICOS S, GEORGESCU C, TUTUNARU D. Multiple benign symmetric lipomatosis—a differential diagnosis of obesity. *Chirurgia (Bucur)* 2013; 108: 580-583.
- 22) AHUJA AT, KING AD, CHAN ES, KEW J, LAM WW, SUN PM, KING W, METREWELI C. Madelung disease: distribution of cervical fat and preoperative findings at sonography, MR, and CT. *AJNR Am J Neuroradiol* 1998; 19: 707-710.
- 23) ADDOLORATO G, MIRIJELLO A, BARRIO P, GUAL A. Treatment of alcohol use disorders in patients with alcoholic liver disease. *J Hepatol* 2016; 65: 618-630.
- 24) FEDERICO A, COTTICELLI G, FESTI D, SCHIUMERINI R, ADDOLORATO G, FERRULLI A, MERLI M, LUCIDI C, MILANI S, PANELLA C, DOMENICO M, VANTINI I, BENINI L, UBALDI E, ROMANO M, LOGUERCIO C. The effects of alcohol on gastrointestinal tract, liver and pancreas: evidence-based suggestions for clinical management. *Eur Rev Med Pharmacol Sci* 2015; 19: 1922-1940.
- 25) MANICONE PF, TARLI C, MIRIJELLO A, RAFFAELLI L, VASSALLO GA, ANTONELLI M, RANDO MM, MOSONI C, COSARI A, LAVORGNA L, CAPUTO F, D'ADDONA A, GASBARRINI A, ADDOLORATO G. Dental health in patients affected by alcohol use disorders: a cross-sectional study. *Eur Rev Med Pharmacol Sci* 2017; 21: 5021-5027.
- 26) ADDOLORATO G, LEGGIO L, D'ANGELO C, FERRULLI A, MIRIJELLO A, CARDONE C, LESO L, MALANDRINO M, CAPRISTO E, LANDOLFI R, GASBARRINI G. Physical considerations for treatment complications of alcohol and drug use and misuse. In: Johnson BA.ed *Addiction medicine*. Springer Science+Business Media, LLC, 2011; pp. 1115-1145.
- 27) MIRIJELLO A, TARLI C, VASSALLO GA, SESTITO L, ANTONELLI M, D'ANGELO C, FERRULLI A, DE COSMO S, GASBARRINI A, ADDOLORATO G. Alcoholic cardiomyopathy: What is known and what is not known. *Eur J Intern Med* 2017; 43: 1-5.