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Schizophrenic Patient with Drug Induced Liver Injury Initially Misdiagnosed as Wilson's Disease with Final Diagnosis of Celiac Disease

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1. Abstract

Associations between psychiatric symptoms in patients with celiac disease have been described in the literature. We report the case of a schizophrenic patient initially suspected of Wilson disease that was diagnosed with celiac disease in our hepatology unit.

2. Introduction

Celiac disease (CD) is an immune-mediated systemic disorder characterized by chronic inflammation induced by gluten in the small intestine, affecting about 1% of the world's population [1]. Clinical manifestations are heterogeneous, with gastrointestinal symptoms being only one sign of a systemic disease. More than half of adult patients present with prominent non-classical extra-intestinal symptoms, such as dermatitis, high levels of aminotransferases, neuropathies and psychiatric disorders [1-5]. Symptoms can be variable and untypical, with gastrointestinal manifestations missing, making the diagnosis challengingand delaying necessary treatment, in particular if confounding factors divert diagnostic attention. This paper presents a case of a schizophrenic patient initially misdiagnosed as Wilson's disease that was diagnosed with celiac disease in the hepatology unit.

3. Results

The patient was a 19-year-old male, presenting with a variety of symptoms of known paranoidschizophrenia, including imperative voice hearing and optical hallucinations, despite ongoingpharmacological treatment. The patient had been jailed for several months for murder of a relative. Routine diagnostic testing in the context of initial manifestation of psychiatric symptoms had revealed increased transaminases (ALAT 530 U/L, ALAT 191 U/L). Further assessment showed low ceruloplasmin (0,11 g/l) and increased urine copper excretion in a primary sample (431 ug/24h). The patient was thus referred to our hepatology outpatient clinic for further evaluation of Wilson disease.

At the time of presentation in our clinic, the patient's predominant clinical signs were apathy, slowed thinking, partial memory loss, aboulia, and dysthymia. He had no signs of ataxia, dysarthria, or tremor. No current or past gastrointestinal symptoms or weight loss were reported. Family history with regards to autoimmune diseases was unsuspicious. BMI was within reference range. No Kayser-Fleischer ring was present. Medication included quetiapine and paliperidone. Clozapine and Olanzapine had been stopped several weeks before presentation. Patient characteristics are summarized in (Table 1). Laboratory testing revealed only slightly elevated transaminases compared to earlier results (AST 57 U/L, ALT 89 U/L), cholestatic parameters and liver function (INR, albumin) were normal (Table 2). Ceruloplasminwas slightly below reference level (0.12 g/l) and serum copper was decreased (8.1 umol/l). However, a repeated urine copper test was within refer-

ence range. Blood tests showed no signs of autoimmune or viral hepatic disease. Hemoglobin was 162 g/l. There were no signs of iron deficiency. IgG and IgA, albumin and levels of vitamin B12 and folate were at normal levels. Abdominal ultrasound showed a normal liver parenchyma with a slight splenomegaly (13 cm). An MRI of the brain did not reveal any structural abnormalities. For further evaluationwe performed a liver biopsy, with histology revealing no evidence of acute or chronic liver disease, in particular no histologic changes suggestive of Wilson's disease. Follow up blood samples showed liver tests return to normal. A repeated urinary copper excretion (with and without D-penicillamine) at the time of liver enzyme normalization was unremarkable. Genetic testing was not performed.

Serologic evaluation for hepatic disease in our clinic includes anti-transglutaminase antibodies (ATA). ATA levels in this patient were >2.600 CU and the patient was referred for an endoscopy, which showed a cobblestone pattern of the duodenum, suggestive of celiac disease (Figure 1). Duodenal biopsies showed significant villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis (>30 lymphocytes / 100 enterocytes) in the bulb and duodenum,compatible with stage IIIb (Marsh-Oberhuber classification, Figure 2), thus confirming celiac disease. A gluten free diet was initiated, which did not immediately improve psychoticsymptoms. 9 months after the initial diagnosis, the patient was still under a therapy with paliperidone on the psychiatric ward. ATA levels almost normalized with a titer of 29 CU (normal range < 20 CU), suggesting adherence to dietary restrictions. However, endoscopic re-evaluation has not yet been performed. Therefore, histologic improvements, in particular villous atrophy, could not be assessed [6]. The next steps would be to verify adherence to thegluten-free diet with a specialized dietitian and performing an upper endoscopy with biopsiesone to two years after the first diagnosis since this patient did not respond to the treatment and seroconversion does not necessarily exclude minor dietary gluten contamination and ongoing intestinal inflammation. The median time to mucosal healing under gluten-free diet has been reported to be up 6 months to 5 years with a median of 1.3 years [7,8].

Table 1: Patient characteristics

Year of birth and age at referral	1999, referral at the age of 19
Sex	Male
Origin and ethnicity	Europe, caucasian
Preexisting conditions	Paranoid schizophrenia
Medication	Quetiapin (max. 100mg/d), Paliperidon (18mg/d), Folic acid (5mg/d), Vit. D3 (10 drops)
Substance abuse	Cigarettes (10/d), Alcohol (0.5-1 bottle of wodka/d), Cannabis (1x/Week), occasional nasal drugabuse
Reason for referral	Suspected M. Wilson
Family history	none
Final diagnosis	Celiac disease

Table 2: Laboratory results

Value	Unit	Ref. range	05.02.2019	07.02.2019	26.03.2019	24.04.2019	13.05.2019	20.05.2019	12.06.2019	03.03.2020
ASAT	U/L	< 50	176	191	57	26	-	25	20	-
ALAT	U/L	< 50	406	531	89	49	50	46	28	-
Ceruloplasmin	g/L	0.15 –0.30	-	-	0.12	-	-	-	-	-
Serum copper	µmol/L	13 – 30	-	-	8.1	-	-	-	-	-
INR		0.7 – 1.2	1.03	-	1.06	-	-	-	1.0	-
ATA-Antibodies	U/ml	< 20.0	-	-	2628.4	-	-	-	-	29

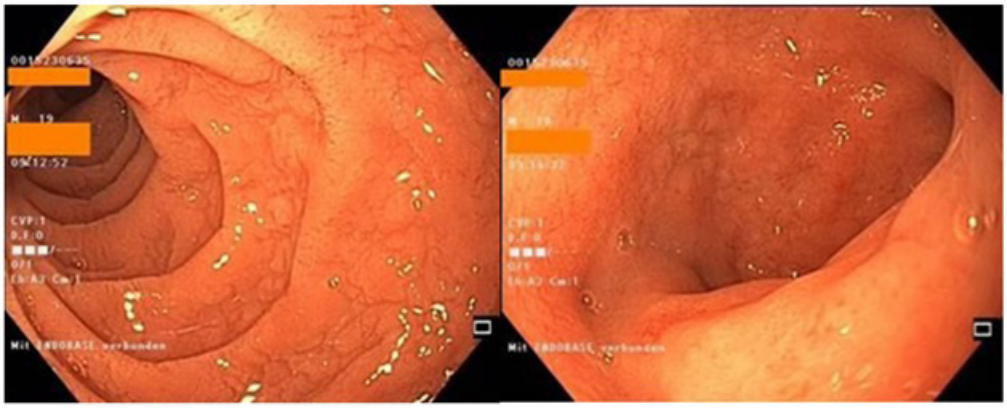

Figure 1: Endoscopic pictures showing the typical abnormalities in the duodenum such as scalloping of duodenal folds, mosaic mucosal pattern and mucosal atrophy.

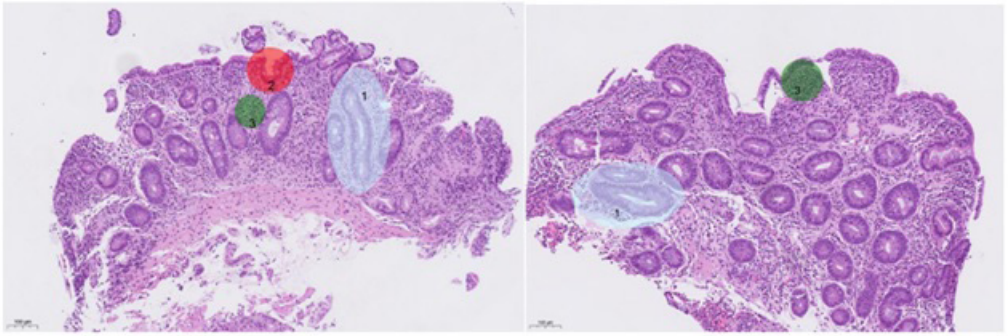

Figure 2: Histological findings of the duodenum and bulb. Duodenal mucosal fragments with the hallmarks of the Marsh-Oberhuber classification which are as follows:

1. marked crypt hyperplasia (marked in light blue).
2. villous atrophy (marked in red, only visible in the upper picture)
3. proliferation of intraepithelial lymphocytes (>30 lymphocytes/100 enterocytes) and of the lymphoplasmocytic infiltrate in the lamina propria (marked green)

4. Discussion

Our case describes a difficult diagnosis of celiac disease due to complex clinical presentations. Initial transaminase elevations led to further evaluation of liver disease. Abnormalities in copper tests with decreased serum copper and ceruloplasmin and increased urinary copper excretion was suggestive of Wilson's disease. Only differential testing for other liver diseases led to the diagnosis of celiac disease. The patient did not show any typical manifestations of celiac disease, in particular no gastrointestinal symptoms or signs of malnutrition, apart from significant psychic disturbances. With this kind of atypical presentation, schizophrenia may be the only manifestation of the underlying disease, highlighting the variable clinical features of a systemic disease.

Psychiatric symptoms in patients with celiac disease have been described in the literature [5]. In particular, associations between celiac disease and schizophrenia have been suggested in since the 1950s [9,10]. Case reports and epidemiological studies indicate a role of celiac disease in the pathogenesis of schizophrenia [11,12]. An interplay between genetic and environmental factors has been assumed, with a possible involvement of the gut-brain axis, triggered by autoimmunity and inflammation [13,14]. Epidemiological data from Taiwan and Denmark suggest an increased risk of schizophrenia in patients with celiac disease, while Swedish data found an association between celiac disease and non-schizophrenic psychosis [3,15-19]. Retrospective data from the United States found higher titers of anti-gliadin antibodies and ATA in schizophrenic patients than in the normal population, though the differences were not clinically significant [20]. Several reports of clinical improvements of schizophrenia after onset of a gluten free diet have been published, though knowledge regarding its effect and latency time to detect it remain limited [21,22]. Some reports indicate clinical improvements in non-schizophrenia neuropsychiatric symptoms after several months [12]. Observational studies of a gluten free diet on schizophrenic patients *without* confirmed celiac disease have given mixed results [23]. There is still insufficient data on patients with concomitant celiac disease [24]. One study has shown that decreasing levels of ATA were associated with improvement of cognitive assessment tests in patients with celiac disease [25]. In our case, the chronic condition of schizophrenia could mitigate dietary effects and delay potential

improvement.

Liver enzymes remained normal after clozapine and olanzapine had been stopped, suggesting drug induced liver injury (DILI) as the likely cause of initial transaminase elevation. Clozapine shows a likelihood score of B on LiverTox with typically hepatocellular injury pattern, while elevations of liver enzymes occur in 10 to 50% of patients taking Olanzapine [26,27]. We suspect that the disorder in copper tests – low serum copper, low ceruloplasmin, high urinary copper in first testing – is associated with DILI in this case. As the patient had been in custody for several months, protein malnutrition as a cause of copper deficiency is possible, but unlikely. To our knowledge, only a few case series have been published investigating copper deficiency in liver disease [28,29]. For our patient we suggest an association of copper tests to hepatic injury, with possible cytolysis or redistribution of copper other body compartments increasing urinary copper excretion [28,30]. However, the exact mechanisms remain unclear.

With significant psychiatric improvement missing in the first months after onset of gluten free diet, clinical presentation is not yet sufficient to suggest a causal association between the two entities. However, it was only due to psychiatric symptoms that diagnostic testing was performed, leading to the diagnosis. Further research of the role of gluten for schizophrenia pathogenesis is needed. In particular, long term follow up of patients with concomitant celiac disease under gluten-free diet is necessary to track potential clinical ameliorations. Clinicians should be aware of the potential association and encouraged to consider celiac disease as a differential diagnosis in schizophrenic patients presenting with elevated liver enzymes or those that do not respond well to psychiatric treatment. Raised urinary copper excretion should be interpreted carefully, as it can be expression of various liver diseases.

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