Correspondence

Hepatic encephalopathy: A call to action to optimize patient outcomes

Dear Editor,

Hepatic encephalopathy (HE) is a debilitating complication of advanced chronic liver disease (ACLD), which severely impacts on health-related quality of life and survival [1,2]. Since there are no universally accepted standards, clinical management of HE is often dependent on local guidelines and personal views.

The Time to DeLiver campaign has been initiated by the European Liver Patients Association (ELPA) to drive change in the perception of HE among healthcare professionals (HCPs), the public, payers and policy makers.

The objectives are to:

1. provide support for patients and carers to combat stigma and drive recognition of HE.
2. support HCPs in identifying HE and thus reducing rates of recurrent episodes and hospital admissions.
3. ensure the patient voice is heard on European level by putting HE on policy makers’ agendas.

A meeting was held in May 2015 in London, UK, with patient organizations, consultant hepatologists and clinical nurse specialists to gain insights on patient perspectives of living with HE and existing local country guidelines.

We developed the ‘Getting a Grip on HE’ report, which announced clear ‘calls to action’ to Members of the European Parliament, European policy makers, the media and stakeholder partners. We are submitting this letter to Digestive and Liver Disease to raise awareness of this initiative in the Gastroenterology and Hepatology medical community.

Burden of HE: An important barrier to the collection of data about the prevalence of HE is the lack of a specific International Classification of Diseases (ICD) code for HE. A severe complication of cirrhosis, such as for example variceal bleeding, precipitating HE may receive a code for the gastrointestinal haemorrhage, but not for HE.

Stigma of HE: Patients with higher levels of perceived stigma have less social support, are less likely to seek medical care, suffer higher rates of depression and have worse quality of life [3]. Addressing these issues would improve individual patient’s lives and those of their family and caregivers.

Multi-disciplinary care: Patients with HE often receive fragmented care that is inadequately coordinated due to a lack of on-site facilities or clear referral pathways [4]. A more coordinated care approach would increase patient attendance at outpatient centres and quality of care.

Identifying patients with HE: Up to 64% of patients die within 1 year of the first diagnosis of HE. One of the barriers to identifying patients with HE and administering appropriate treatment may be the lack of knowledge and skills among primary HCPs. An example of competence framework describing the knowledge, skills and attitudes that are required to deliver patient-centred liver care has been recently published [5].

Treatment: Treatments for HE are available which improve patient outcomes, but the most important aspect of HE management is prompt recognition and treatment of precipitating factors. Unfortunately, not all treatments are available or reimbursed.

Calls to action

In response to the challenges outlined above, we identified a number of barriers and developed a series of ‘calls to action’ (Fig. 1) to ensure the inclusion of HE within public-facing information and to improve quality of care for patients.
Conclusions

By addressing the ‘calls to action’, HCPs, patient associations and governments will be able to recognize and address potential barriers to diagnosis and treatment of HE. A more coordinated and multidisciplinary approach will facilitate the development of easily applicable guidelines defining the best practice care and support for people with HE. This will ultimately benefit healthcare systems, patients and their carers, and policy makers.
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References

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Colonic small cell neuroendocrine carcinoma in a patient with long-standing ulcerative colitis treated with azathioprine

Dear Editor,

We report the case of a patient with long-standing ulcerative colitis (UC) treated with Azathioprine (AZA) who developed a neuroendocrine small cell carcinoma arising from the sigmoid colon.

A 61-year old man was diagnosed with extensive UC in 2002. After initial response to oral and topical mesalazine, azathioprine (AZA) 2.5 mg/kg/day was added five years after diagnosis because of steroid-dependency. After AZA introduction the patient achieved sustained steroid-free remission but, 3 years later, he was diagnosed with idiopathic autoimmune hemolytic anemia requiring repeated steroid courses despite concomitant immunosuppression. Eight years after diagnosis the patient was in remission off-steroids and endoscopic surveillance for long-standing disease was started. At index colonoscopy (2010) erythema and decreased vascular pattern were observed in the whole colon except for the sigmoid which showed also mild friability and small erosions. Histological examination was consistent with UC in remission with features of mild activity in the sigmoid colon. No dysplasia was observed. Endoscopic surveillance was then planned every 2 years and the subsequent colonoscopy (2012) showed a similar pattern. In 2014 the patient was symptom-free but a routine abdominal ultrasound prescribed by the general practitioner showed multiple liver metastasis. A total body CT scan confirmed metastatic liver disease without any evidence of primitive neoplasm. A bowel wall thickness of the sigmoid colon with nodular mucosa and confluent deep ulcerations: histologic examination of endoscopic biopsies showed a small cell neuroendocrine carcinoma with high proliferative index (Ki67 > 90%). Immunohistochemical analysis showed expression of thyroid transcription factor-1 (TTF-1), pool of cytokeratins and synaptophysin and absence of CDX2 and CD20 antigens. These immunohistochemical findings were confirmed by histological examination of a percutaneous liver biopsy (Fig. 1). An intestinal origin of the neoplasm was supposed considering the absence of any lesion in the lung. In the subsequent weeks a clinical deterioration occurred with rapidly progressive liver failure. Death occurred within 2 months from diagnosis.

Neuroendocrine neoplasms (NENs) account for less than 1% of all colorectal malignancies and are characterized by a high rate of liver metastasis: the prognosis is particularly poor compared to colorectal adenocarcinoma [1]. NENs occur infrequently in the setting of inflammatory bowel disease (IBD), and the vast majority are clinically indolent, well-differentiated carcinoids found incidentally after surgery. Rarely NENs other than carcinoids have been reported in IBD and a neuroendocrine differentiation from multipotential cells in dysplastic epithelium has been suggested [2].

The case we have described shows some interesting peculiarities. Firstly the neoplasm was diagnosed at an advanced stage despite biannual endoscopic examination: this may reflect the rapid rate of malignant progression and/or the suboptimal negative predictive value of endoscopic surveillance.

Secondly the immunohistochemical finding of TTF-1 expression. TTF-1 is a tissue specific transcription factor that plays a critical role in the normal development of embryonic epithelial cells of the thyroid and lung and it is commonly used to assist in the differential diagnosis of carcinomas of the lung and thyroid. Recent studies, however, have reported that TTF-1 can infrequently be found to be expressed in some NENs arising in other organs, including the colon [3]. The prognostic significance of TTF-1 expression is controversial. In small cell lung cancer TTF-1 has no prognostic value but it may be associated to improved outcome in non-small cell lung cancer [4].

Finally, a potential role of AZA in promoting tumor occurrence or its rapid progression cannot be excluded. The patient had been receiving AZA for 7 years because of steroid dependency and the development of malignancy as a late complication of thiopurine-use is of major concern. Although an increased risks of lymphoproliferative disorders and non melanoma skin cancer is well established, data on the overall cancer risk are limited and controversial. Recently, an historical cohort study showed that AZA use in IBD patients is associated with an increased risk of overall cancer although causality cannot be established [5]. However, a specific association with thiopurine exposure and NENs has never been reported.