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**LETTER TO THE EDITOR**

# Carcinoid encephalopathy: A single entity or a spectrum of different disorders?

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**To the Editor,**

Hormone releasing carcinoid tumors usually produce a variety of symptoms like abdominal pain, diarrhea, wheezing and flushes. These symptoms, also known as the carcinoid syndrome, are caused by the overproduction of serotonin. In most cases they can be successfully treated with somatostatin analogues. As described in some case reports, patients with a carcinoid tumor can develop an encephalopathy, although this condition remains very rare [1–3]. Until now, a clear relationship between the carcinoid tumor and the associated encephalopathy has not been established and its treatment remains highly speculative.

We present a new case of carcinoid associated encephalopathy suggesting a hypothesis for the underlying pathophysiological mechanism and a successful symptomatic therapy.

## Case report

In 1991, a 39-year-old male was diagnosed with a carcinoid tumor. The primary tumor was located in the small intestine with multiple metastatic lesions in the peritoneum. All macroscopic intestinal and peritoneal lesions were resected, resulting in an asymptomatic period of nine years. From 2000 till 2008, two relapses with abdominal pain, flushes and intermittent diarrhea occurred. These episodes were treated with surgical resection, intramuscular octreotide (Sandostatine LAR, Novartis) and/or $^{90}$Y-lanreotide (Octreother, SMT 487, Novartis) according to the type of carcinoid lesions that were found by the (111In-DTPA-D-Phe1)-octreotide scintigraphy (octreoscan). Since the treatment with $^{90}$Y-lanreotide in the second relapse had no major effects on the symptoms, a trial with alpha-interferon (Intron A, Schering-Plough, 3 mio units sc, 3 times a week) was performed but had to be stopped after three months because the patient developed an acute psychotic syndrome. As a result, the therapy was further restricted to the administration of Sandostatin LAR. In February 2008, several sessions of radiotherapy over the right clavicular region were performed after the discovery of a new symptomatic lesion. Over the next few months, the carcinoid symptoms gradually increased and only after continuous intravenous administration of Sandostatin, the abdominal pain, flushes and diarrhea were more or less under control. However, only a few months later, the patient developed three episodes with different psychiatric symptoms: severe anxiety, confusion, headaches, attention problems, motor restlessness during night and extreme tiredness at daytime, and feelings of uncontrolled aggression. These symptoms increased during the three to four days and then slowly disappeared. No psychotic symptoms were present. Somatic investigation revealed only a minimal increase of the blood liver enzymes ($<$ 2 times normal), a normal peripheral blood count, normal electrolytes, normal kidney and thyroid function. No signs of infection were found. The serum levels of chromogranin A and the 5-HIAA dosage during a 24-hour urine collection were both within normal ranges, showing that the production of serotonin was under control with the current treatment of somatostatin (at 6 mg per 24 hours IV). An octreoscan showed no new lesions and the previous liver lesions had disappeared. No central localization of the tumor could be detected on contrast-enhanced

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Table I. Concentration of chromogranin in cerebrospinal fluid before and during treatment with tryptophan.

| | Concentration of chromogranin in CSF (μg/L) |
|---|---|
| Before tryptophan treatment | 736 |
| After 1st month of tryptophan (3 × 500 mg/day) | 725 |
| After 2nd month of tryptophan (3 × 500 mg/day) | 705 |
| After 3rd month of tryptophan (3 × 1000 mg/day) | 779 |

CT and MRI. FDG-PET investigation of the brain and EEG were also within normal ranges. Investigations of the cerebrospinal fluid were negative for anti-Hu, anti-Yo, anti-Rhi antibodies and Borrelia Burgdorferi IgG and showed only a marginal increase of the protein level (60.0 mg/dL, normal between 15–50 mg/dL). Malignant cells were present in the cerebrospinal fluid and chromogranin concentrations were extremely high (e.g., 736 μg/L, 9 to 14 times higher than previously reported maximum levels [4]), suggesting a central nervous (CNS) localization of the carcinoid tumor.

Since carcinoid associated encephalopathy was previously reported to be associated with tryptophan deficiency [2], tryptophan (initially at a dose of 3 times 500 mg/day) was supplemented, although the serum tryptophan of the patient was within normal range. No improvements in symptoms were noticed after three months of tryptophan treatment, even at a double dose. Chromogranin levels in the cerebrospinal fluid also remained the same (Table I). Contrary, the patient was re-admitted with a new episode of psychiatric symptoms. Tryptophan treatment was stopped. Psychiatric symptoms and neuro-cognitive functioning of the patient were in detail assessed by a psychiatrist using a range of different neuro-cognitive tests (Table II). Selective attention and resistance to cognitive interference [5–8], verbal and visual memory [5,7–9], verbal fluency [5,7,8], finger and hand dexterity and psychomotor speed [5,7,8] were severely disturbed indicating important cognitive dysfunctioning. Since the presence of malignant cells and high levels of chromogranin in the cerebrospinal fluid suggested a (microscopic) CNS localization of the carcinoid tumor, it was hypothesized that the psychiatric symptoms of the patient were caused by an intermittent overproduction of serotonin by metastatic carcinoid tumor cells in the brain. Therefore, a treatment of risperdone was started because of its strong serotonin-2a receptor blocking properties.

The improvement of the psychiatric symptoms was remarkable and the neurocognitive functioning three months after the start of risperdone treatment improved until normal range (Table II).

## Discussion

The development of an encephalopathy is a rare condition in patients with carcinoid tumor. Different underlying mechanisms have been proposed. Some reports suggest that a carcinoid encephalopathy stems from a disequilibrium of tryptophan metabolism in which a large proportion of the body's tryptophan may be shunted into the tumor activity peripherally, causing a lack of this substance in the central nervous system [2]. Since a trial with tryptophan supplementation did not result in any improvements, and even may have worsened the psychiatric symptoms, it is unlikely that tryptophan deficiency has contributed to the psychiatric symptoms in this patient.

Secondly, some authors have described a metabolic encephalopathy in patients with carcinoid tumors who suffer from massive hepatic metastases and fulminant liver failure [3]. Again, little arguments are available to support this hypothesis: blood liver enzymes were only little increased and no major hepatic metastases could be found. Thirdly, ACTH- or CRH- secreting carcinoid tumors may result in a Cushing syndrome [1]. Beside the typical cushingoid features, these patients experience a wide range of emotional changes ranging from irritability to psychosis as a result of the hypercortisolism. The 24 hours urine cortisol and serum ACTH of this patient were within normal range and the patient did not suffer clinically from a Cushing syndrome. Finally, the patient had also no signs of Pellagra and his EEG was normal, excluding other forms of encephalopathy [1].

However, this case-report may suggest another possible underlying mechanism of carcinoid associated

Table II. Neuro-cognitive test results of the patient before and after start of treatment with risperdone.

| | Psychological test | baseline | 3 months after start of risperdone | normal range |
|---|---|---|---|---|
| Explicit verbal memory | Rey Auditory Verbal Learning Test | 29 | 48 | >44.9 |
| Visual memory | Visual association test | 17 | 23 | >22–23 |
| Verbal fluency | Controlled oral word association test | 12 | 19 | >19.2 |
| Selective attention and resistance to cognitive interference | Stroop Coloured Word test | 86 | 58 | <50 |
| Finger and hand dexterity | Purdue Pegboard test | 8.33 | 10.66 | >10.2 |

Baseline = before start of treatment with risperdone

encephalopathy. In this patient, the metastatic carcinoid tumor was peripherally under control with the continuous IV administration of octreotide. Since serotonin does not cross the blood-brain barrier and octreotide only passes in a small amount [10,11], it is likely that the carcinoid tumor had spread to the brain. The episodic overproduction of serotonin by the cerebral metastasis may produce the sudden episodes of psychiatric symptoms including aggressive behavior, cognitive impairment, motor restlessness, agitation, nighttime insomnia, attention problems, increased appetite and headaches. This may also explain the worsening of the psychiatric symptoms after tryptophan supplementation. Although no macroscopic abnormalities were found on CT, MRI and FDG-PET, the extremely high concentration of chromogranin and the presence of malignant cells in the cerebrospinal fluid support this hypothesis. Further, the peritoneal metastasis, which was only visible during the surgery and not on any imaging, were widespread and very small. It may be possible that the CNS metastasis have adapted a similar form or pattern as the peritoneal metastasis since they were also not detectable by brain imaging. To further support this hypothesis, the level of 5-HIAA in the cerebrospinal fluid was determined and was also elevated, although not as spectacular as the chromogranin concentration (147 nmol/L, normal between 45–135 nmol/L). If the lesions could be confirmed, an etiologic treatment could be pancranial irradiation to inactivate the lesions. This possibility was discussed with the patient but refused as pharmacological treatment with risperdone rendered him asymptomatic.

## Conclusion

Carcinoid associated encephalopathy has frequently been reported as an important secondary consequence of peripheral carcinoid tumor activation. Different underlying mechanisms such as tryptophan deficiency, hypercortisolism or severe liver failure have been proposed. However, this case-report suggests that the development of a carcinoid associated encephalopathy may also be associated with an overproduction of serotonin in the central nervous system caused by cerebral carcinoid metastatic activation, which can be symptomatically treated by serotonin-2a receptor antagonism.

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