Patients With Carcinoid Syndrome Exhibit Symptoms of Aggressive Impulse Dysregulation

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Objective: Carcinoid tumors can produce excessive amounts of biogenic amines, notably serotonin. We assessed psychiatric symptoms in carcinoid patients and peripheral metabolism of tryptophan, the precursor of serotonin. **Methods:** Twenty consecutive patients with carcinoid syndrome underwent a structured psychiatric interview applying DSM-IV (Diagnostical Statistical Manual) criteria. Tumor activity was measured by determination of 24-hour urine excretion of 5-hydroxyindoleacetic acid (5-HIAA) and platelet serotonin levels. Plasma tryptophan levels were measured and compared with sex- and age-matched references. **Results:** Fifteen patients (75%) fulfilled diagnostic DSM-IV criteria for a disorder of impulse control. Tryptophan plasma levels were lower in patients compared with controls ($p = .031$) and were correlated negatively with urinary 5-HIAA excretion ($p = .001$). **Conclusions:** Impulse control disorders are prevalent in patients with carcinoid syndrome. The serotonin production by the tumor possibly decreases the tryptophan pool in the cerebrospinal fluid, which is the essential substrate for the production of brain serotonin as a pivotal neurotransmitter. **Key words:** carcinoid; serotonin; aggression; tryptophan.

5-HIAA = 5-hydroxyindoleacetic acid.

Carcinoids are neuroendocrine malignancies derived from cells characterized by their ability to produce and secrete serotonin. Peripherally produced serotonin cannot pass the blood-brain barrier. Excess of serotonin causes diarrhea and flushing when liver metastases are present or when the tumor originates from organs not draining into the portal circulation. The so-called carcinoid syndrome usually develops many years after onset of the disease. Because of the relatively long survival and indolent course of the disease, quality of life is an important treatment issue. Carcinoids are divided into foregut (respiratory tract, stomach, duodenum, and pancreas) midgut (ileum and appendix) and hindgut (left colon and rectum). Tumors originating from the midgut are especially active serotonin producers (1). Patients with disseminated disease undergo (palliative) surgery and/or are treated with somatostatin analogues or interferon-α (1). Beside physical discomforts, serotonin overproduction can result in emotional disturbances. Case reports indicate a relationship between carcinoid and depression, anxiety symptoms, hostility, sleeping disorders, and psychosis (2–4). Major et al found in 22 carcinoid patients that 50% exhibited depressive symptoms (5). In a study in carcinoid patients, of which 18 showed elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion, 2 cases of depression were reported (6). In a more recent study, no relation between measures of depression and anxiety and tumor neuroendocrine activity were found (7). In contrast with the present study, both studies included carcinoid patients regardless of the presence of carcinoid symptoms. Previous studies diverge strongly both in the nature and prevalence of reported symptoms. These reports have focused on psychiatric syndromes such as depression and anxiety and have not applied DSM-IV criteria for objective psychiatric diagnosis. In the present study, we observed that personality changes, with patients showing aggressive behaviors, are highly prevalent in carcinoid syndrome patients. Moreover, we tested whether these psychiatric symptoms are related to the metabolic activity of the carcinoid as measured by plasma tryptophan and platelet serotonin levels and urinary 5-HIAA excretion.

METHODS

Patients

Patients with histologically proven midgut carcinoid tumor, leading to carcinoid syndrome, visiting the Department of Medical Oncology, University Hospital Groningen, were asked to participate in this study. Additional criteria were: older than 18 years of age, verbal adequacy, ability to perform diagnostic tests, life expectancy over 6 months. The study was approved by the local medical ethical committee. All patients gave written informed consent after complete description of the study. As controls served patients suffering from hepatitis C or Crohn disease. These patients were recruited for another study by our group and were not selected. However, hepatitis C patients with a history of substance abuse were excluded.

Psychiatric Assessment

Patients and controls were assessed by a structured diagnostic interview by a psychiatrist (JB) that took approximately 90 minutes (8). In this interview, the full scope of major DSM-IV disorders such as depression, anxiety, and psychosis was addressed. Patients were invited to take along their spouses. The structured interview in which current DSM-IV diagnosis was made, was followed by an interview in which premorbid personality, course of the illness, and the relation with psychiatric comorbidity, when present, was assessed. The interviewer was blind to the biochemistry and not preoccupied by any hypothesis. He was, however, not blind to the diagnosis of the patients. This was not possible because duration and course of the illnesses were part of the interview. Furthermore, carcinoid patients are easy to recognize because most of them show typical skin reactions, especially in the face. Diagnoses were based on DSM-IV criteria.

Biochemical Measurements

The 24-hour urine samples were collected using 2 l brown polypropylene bottles (Sarsted, Nuembrecht, Germany) containing 250 mg each of $Na_2S_2O_5$ and EDTA as preservatives. Urine samples were acidified to pH 4.0 with acetic acid and stored at −20°C. Venous blood samples were collected in vacutainer tubes containing 0.12 ml (0.34 mmol/l) EDTA solution. Plasma samples, after centrifugation, were stored at −20°C until analysis. The quantification of urinary 5-HIAA, total plasma tryptophan, and platelet-rich plasma serotonin was performed with methods based on high performance liquid chromatography with fluorometric detection (9,10). Urine samples were collected in the 24 hours preceding the visit to the clinic in which the plasma samples were taken and the psychiatric interviews took place.

For platelet-rich plasma levels of serotonin and urine levels of 5-HIAA,

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reference ranges of 2.8 to 5.4 nmol/10^9 platelets and 0.8 to 3.8 mmol/mol creatinine were sustained respectively (10). For the assessment of total 24-hour excretion of 5-HIAA, urinary creatinine level was measured. All plasma samples were taken between 10 and 12 AM. Control subjects were not recruited for this study but were taking part in a study performed simultaneously by our group in which plasma tryptophan and platelet serotonin were also measured. The urinary 5-HIAA was not measured, but reference values are available.

Statistics

Plasma levels of tryptophan and platelet serotonin in patients and controls were compared using the 2-tailed paired Student's t test. Total 24-hour excretion of 5-HIAA in μmol was computed out of 24-hour urinary levels of 5-HIAA/mmol creatinine. Total 5-HIAA excretion was correlated to plasma levels of tryptophan in patients by the Spearman rank test. Platelet serotonin content was correlated to plasma tryptophan levels in patients by the Spearman rank test. The differences in the number of patients suffering from psychopathology in carcinoid and control patients was computed by the chi-square test. Also, a chi-square test was performed to compare total 24-hour 5-HIAA excretion in carcinoid patients suffering from aggressive personality change vs. patients who did not. Plasma tryptophan levels between these groups were compared using analysis of variance.

RESULTS

Twenty of twenty-three eligible patients participated in the study (Table 1). Eleven were male, nine female. Age ranged from 46 to 76 years, with a mean age of 61 years. Treatment consisted of subcutaneous octreotide in 12 patients (dose range, 0.1–0.6 mg/d) and subcutaneous interferon-α in 2 patients (2.5 million U/d), while 2 patients used both drugs. Three patients occasionally took 10 mg of oxazepam before sleeping; 1 patient used the antidepressant amitriptyline.

All patients previously established increased urinary 5-HIAA excretion and 18 patients exhibited urinary levels of 5-HIAA of at least 5 mmol/mol creatinine at the interview. In carcinoid patients plasma tryptophan levels ($N = 20$; mean 42.6 ± 12.6 mmol/l) were lower compared with controls ($N = 20$; mean 51.07 ± 5.7; $t = 2.40$; $df = 19$; $p = .026$). Platelet serotonin level was increased in patients (mean 24.9 ± 10.7) compared with controls (mean 2.7 ± 1.2; $t = 8.9$; $p < .001$). In carcinoid patients, a significant negative correlation did exist between total 24-hour urinary excretion of 5-HIAA (mean 440 μmol, see Figure 1) and plasma tryptophan levels ($N = 20$; $r = -0.66$; $df = 19$; $p = .001$). No correlation was observed between the platelet serotonin content and plasma tryptophan level. For 19 patients, the psychiatric interview was their first, and it usually took at least 20 minutes before psychiatric symptomatology could be discussed. Fifteen patients were accompanied by their partner. Controls (11 male, 9 female) were suffering from Crohn disease ($N = 7$) or viral hepatitis C ($N = 13$). Their age ranged from 28 to 59 years with a mean of 52 years. Five controls were accompanied by their partner.

In 15 carcinoid patients (8 male, 7 female), increased expression of aggressive impulses was reported leading to disturbed social functioning, which discriminated them strongly from the control group ($df = 1$; $p = .008$). This symptomatology reached DSM-IV criteria, and the patients were diagnosed as having a personality change due to a medical disorder (DSM-IV code 310.1). The main criteria for this diagnosis were the persistent character of the personality change and the associated functional impairment. These patients were characterized by high expression of verbal aggression in social or vocational situations in a manner, which was described by patients and their spouses as "not fitting to the patients former personality." Severity ranged from increased irritability at home to verbal offense at work. All employed patients suffering from this complaint ($N = 6$) had serious

TABLE 1. Demographical, Medication, and Treatment Data of Patients

Sex	Age	Medication	Urinary 5-HIAA (μmol/24 hr)	Platelet Serotonin (nmol/10^9 platelets)	Plasma Tryptophan (mmol/L)	Impulse Control Disorder
F	68	Octreotide	16.3	6.3	62	+
F	46	Octreotide	1045	17	22	+
F	57	Octreotide	726	29	29	+
M	59	Octreotide, interferon	209	31	30	+
M	59	Interferon	364	22	43	+
M	56	Octreotide	160	33	62	+
M	65	Octreotide, amitriptyline	183	23	51	+
F	75	Octreotide	109	28	48	+
M	65	Octreotide	42.5	19	59	−
F	75	Octreotide	85.6	17	43	−
F	65	Octreotide	414	22	56	+
F	61	None	531	14	36	−
M	57	Octreotide	460	32	47	+
M	52	None	218	16	57	−
M	57	Octreotide, interferon	171	31	29	+
F	71	Octreotide	94.4	39	57	+
M	64	Interferon	341	36	30	−
M	55	Octreotide	2952	45	28	+
F	76	Octreotide	5.9	3.9	50	+
M	49	Octreotide	661	33	40	+

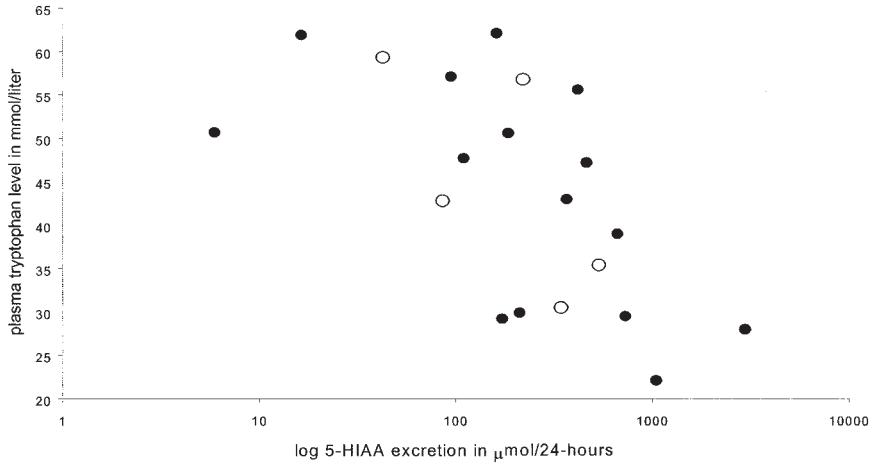

Figure 1. Plasma levels of tryptophan correlate negatively with 24-hour urinary excretion of 5-HIAA in carcinoid patients ($p = .001$; $r = -0.66$). Open dots refer to patients not suffering from impulse control dysregulation.

problems at work. One patient, who was a managing director, had become so aggressive that employees avoided him. This patient finally had to quit his job. Another patient lived in the constant fear of impulsively killing his wife, a fear that was shared by her. Twelve of 16 married patients exhibited marital problems. All patients experienced these complaints as severe handicaps in social functioning. No contact with the law was reported. The increase in impulsivity was first noted by the partners of the patients. All diagnostic information acquired from spouses was only taken into account when confirmed by the patient. The aggressiveness is marked by impulsivity, as patients feel regret shortly after an offense is made. In most cases, the symptoms of decreased impulse control preceded typical carcinoid symptoms such as flushing and diarrhea. The change in personality was retrospectively reported usually before the tumor was diagnosed. In carcinoid patients, no relationship between plasma levels of tryptophan ($df = 18$; $p = .84$) or total 24-hour 5-HIAA excretion ($df = 19$; $p = .40$) and the presence of aggressive personality change was established. No psychotic symptoms, ie, hallucinations and delusions, were found in any of the patients. Three patients were suffering from anxiety symptoms; none of them, however, reached the criteria for a DSM-IV diagnosis.

Depressive symptomatology consisting of mild dysthymia, which again did not reach DSM-IV diagnostic criteria, was found in 5 patients. One of these patients, who also suffered from symptoms of aggressive personality change, used the antidepressant amitriptyline without effect on any of the symptoms. Two patients received interferon-α treatment.

One patient suffering from hypersomnia slept 16 hours a day. In this woman, no psychiatric symptoms were present. In control patients, no structural psychopathology was observed. Two of them were suffering from mild depression. One of them was diagnosed with borderline personality disorder.

DISCUSSION

The present study demonstrates that, in patients with carcinoid syndrome, personality changes marked by aggressive impulse dysregulation are frequent. This finding is in line with the study of Patchell and Possner (6), which reported normal prevalence of depressive symptoms in carcinoid patients. Most previous studies used psychometric scales based on DSM-described pathologies. However, it could well be that somatic patients suffering from psychopathology might show symptoms that do not fit regular DSM syndromal classification. These symptoms will be missed easily when patients are examined with fixed psychometric scales. The psychopathology we report in these patients could only be classified as "personality due to a medical disorder." Since this diagnosis lacks any specificity, it will not distinguish between patient groups. It, however, does imply that patients suffered from social invalidation indicating the severity of the disorder. Symptoms of aggressive personality change were usually retrospectively reported before the full expression of the carcinoid syndrome with diarrhea and flushing. This only occurs after dissemination of the tumor into the liver; before this moment, excessive production of serotonin in the gut will be cleared by the portal circulation. Therefore, increased aggression might be the first symptom of the tumor. Depressive symptomatology not reaching DSM-IV status was observed in 5 patients, 2 of whom received interferon-α. Interferon-α treatment itself has been associated with depression (11). In the present study, plasma levels of tryptophan in carcinoid patients were negatively correlated with tumor endocrine activity as measured by 24-hour 5-HIAA excretion. This points to interference of the carcinoid tumor with plasma tryptophan levels. In our patient sample, plasma tryptophan levels did not correlate with impulse control problems. This is possibly due to physiological fluctuations of plasma tryptophan levels. In contrast, psychiatric diagnoses were made on the basis of symptoms over the last 4 weeks. Platelet serotonin levels were high in carcinoid patients. This is related to peripheral overproduction of serotonin by the carcinoid tumor. We propose that a relation may exist between symptoms of aggressive impulse dysregulation and excessive peripheral production of serotonin by the carcinoid tumor. Under physiological circum-

stances, serotonin cannot pass the blood-brain barrier and cerebral serotonin synthesis is highly dependent on availability of the precursor, the essential amino acid tryptophan (12). It might well be that in brain tissue, a serotonergic dysfunction is due to peripheral consumption of the precursor tryptophan. Cerebral uptake of tryptophan is independent of cerebral demand, but it is determined by the ratio of plasma tryptophan vs. the other large neutral amino acids competing for passage over the blood-brain barrier (12). Our findings are in line with reports of increased hostile reactions in healthy subjects undergoing acute tryptophan depletion (13,14). In vervet monkeys, CSF levels of 5-HIAA are inversely correlated with social impulsivity (15). Low cerebral serotonin levels have been associated with aggressive suicide attempts, impulsive arsonism, and with outwardly directed hostility in personality disorders (16,17). In fact, this feature is associated with (auto)aggression regardless of diagnosis (18). The relation between the cerebral serotonergic system and impulsive aggression has recently been reviewed (19). Our observations of impulsive aggression in social situations fit within such a specific aberration of the serotonergic system. Tryptophan depletion might occur in many somatic states such as inflammatory diseases or patients undergoing treatment with recombinant interferon-α (20). Unfortunately, no structural research has been performed to investigate possible aggressive behaviors, although irritability is frequently observed in such patients (21).

Occurrence of impulse control disorders has not been reported before in carcinoid patients. Symptoms of disordered aggressive impulse control are hard to detect because most clinicians and researchers focus on symptoms of mood, anxiety, and psychosis, for which in these patients no differences were observed with the general population. Another difficulty in diagnosing aggressive impulse dysregulation is the reluctance of patients to discuss these issues, because they may have led to marital and social problems. Interpersonal problems, however, can provide appropriate entrance to the discussion of aggressive behavior. In this regard, it must be noted that aggressive behavior in some controls may be unrecognized because only 5 controls were accompanied by their spouses. In carcinoid patients, the first treatment option should be optimal treatment of the tumor aimed at reducing serotonin production, eg, with octreotide or interferon-α. Treatment options of the psychopathology with antidepressant drugs are limited, because most antidepressants will influence not only central but also peripheral serotonergic metabolism in carcinoid patients. Accordingly, it has been shown that antidepressants may provoke diarrhea and flushing (22). The first option is to provide information about the nature of the symptoms to the patient and his or her relatives, which may help to improve social functioning. Options for medication to treat impulse control problems in carcinoid patients that will be tolerated, ie, not interfering with peripheral metabolism of serotonin by interference with peripheral breakdown or uptake processes, have yet to be developed.

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