Chapter 4
Neuropsychological investigation into the carcinoid syndrome

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Abstract

Rationale: In patients suffering from metastatic carcinoid tumors chronic disturbances of serotonergic metabolism are frequently present. Serotonin is supposed to influence a range of cognitive functions.

Objectives: The present study evaluates the cognitive performance of carcinoid patients.

Methods: In 14 patients with proven carcinoid syndrome neuropsychological functioning was studied. Visual search, sustained attention, set shifting ability and spatial working memory were assessed using tests from the CANTAB neuropsychological battery. This was compared with performance of matched healthy controls.

Results: Plasma tryptophan levels were lower compared to controls. Patients showed an enhanced ability to learn new stimulus-response associations. Sustained visual attention however, was impaired.

Conclusion: Cognitive patterns were different from those found in depressive patients and partly mimicked those found in tryptophan depletion experiments. Further investigation has to point out the role of serotonergic changes in the accomplishment of affective states.
Introduction

Carcinoids are the most commonly occurring tumors of endocrine nature in the gastrointestinal tract with an incidence of 1-2 per 100,000. Although carcinoids occur in every age group there is a peak in the sixth and seventh decade. These neuroendocrine malignancies are derived from cells classified to the Amino Precursor Uptake and Decarboxylation system due to their ability to secrete biogenic amines. They are found throughout the body predominantly in the gastrointestinal tract where they are dispersed as single cells in the (sub)mucosal layers. In case of metastatic disease carcinoids are characterized by high secretion of serotonin (5-HT) leading to increased platelet 5-HT content and high excretion of the main metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA). It has been estimated that the tumor contains up to 200 times the normal total body 5-HT and that as much as 60% of all dietary tryptophan may be consumed by the tumor. A consequence could be that the brain becomes deficient in tryptophan thereby affecting neuronal 5-HT synthesis. It is well known that the rate of cerebral synthesis of this amine, in humans, is highly dependent upon the availability of the precursor tryptophan (Bender 1983). In patients with metastatic carcinoid disease a variety of psychiatric complications has been reported. In case reports a relationship between carcinoid and depression, anxiety, hostility, sleeping disorders or psychosis have been described (Hanna 1965; Trivedi 1984). Major et al. found in 22 carcinoid patients, that 50% exhibited depressive symptoms (Major et al. 1973). In a study in 18 carcinoid patients, two cases of depression (11%) were reported (Patchell and Posner 1986). In these studies, diagnoses were made retrospectively.

In humans, there is a limited amount of literature available on the role of the serotonergic system in cognition. Some studies examined the cognitive effects of reduced central serotonergic activity by experimentally depleting healthy subjects from tryptophan, which is the precursor of 5-HT. These studies revealed impairments in visuospatial paired associative learning (Park et al. 1994) and in both visual (Rubinsztein et al. 2001) and verbal delayed recognition (Riedel et al. 1999; Schmitt et al. 2000). With respect to executive function, tryptophan depletion seems to improve focused attention.
and verbal fluency (Schmitt et al. 2000) and the ability to dissociate
incompatible visuo-motor response associations (Coull et al. 1995)
while it disrupts the ability to learn changed stimulus-reward associ-
atations (Rogers et al. 1999). We propose that in carcinoid patients, a
peripheral overconsumption of tryptophan could result in a central
depletion of 5-HT, which in turn induces specific cognitive impair-
ments. This hypothesis was tested by examining performance of
metastatic midgut carcinoid patients on the Cambridge
Neuropsychological Test Automated Battery (CANTAB, Fray et al.
1997). Results will be discussed in relation to those found by trypt-
ophan depletion studies in healthy volunteers and in subjects with
major depression.
Materials and Methods

Subjects
Between September 1999 and July 2000, all patients visiting the Department of Medical Oncology, University Hospital Groningen with histologically proven metastatic midgut carcinoid tumor, leading to carcinoid syndrome, were asked to participate in this study. Additional criteria were: over 18 years of age, verbal adequacy, capable to perform diagnostic tests, life expectancy over 6 months, stable phase of disease. No medication interfering with 5-HT metabolism. Fourteen (8 males, 6 females) out of 17 eligible patients agreed to participate in the study (see table 1). The age of participants ranged from 46-75 years with a mean of 60 years. Treatment consisted of octreotide subcutaneously in 15 patients (dose range 0.1-0.6 mg/day). Verbal intelligence was estimated with the Dutch translation of the National Adult reading test (Schmand et al. 1991). Ten patients were classified according to this test in the group with an I.Q. between 100 and 110 and four with an I.Q. between 110 and 120. Fourteen healthy volunteers matched for sex and I.Q. served as a control group. Their age ranged from 45-69 years with a mean of 52 years. The study was approved by the local medical ethical committee. All subjects gave informed consent after the study procedure had been explained to them.

Biochemical measurements
Venous blood samples were collected between 9 and 12 a.m. 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 total plasma tryptophan in mmol/L, urinary 5-HIAA in mmol/mol creatinine and platelet rich plasma serotonin in nmol/10^9 platelets was performed with methods based on high performance liquid chromatography with fluorometric detection. For platelet rich plasma levels of serotonin, and urine levels of 5-HIAA reference ranges of 2.8-5.4 nmol/10^9 platelets and 0.8-3.8 mmol/mol creatinine were sustained (Kema et al. 1993). In order to establish reference values for tryptophan, blood samples were collected between 9 and 12 a.m. in 14 healthy controls matched for sex and age. These subjects were not recruited for this
study but were taking part in a study performed simultaneously by one of our group members (I.P.K.) for the establishment of reference values for blood tryptophan levels.

**Neuropsychological assessment**
The following four tests from the CANTAB battery were run.

**Intra-/extra-dimensional shift (ID/ED) task**
This task assesses the ability to attend to the specific attributes of compound stimuli, and to shift that attention when required. Two artificial dimensions are used: color- filled shapes and white lines. Two stimuli (one correct, one incorrect) are displayed, initially each of only one dimension, then each of both dimensions (first adjacent, then overlapping). Feedback teaches the subject which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g. color filled shapes remain the only relevant dimension) then later extra-dimensional (white lines become the only relevant dimension). The test consists of 9 stages. These are: 1 simple discrimination, 2 simple reversal, 3 and 4 compound discrimination, 5 compound reversal, 6 intra dimensional shift, 7 reversal, 8 extra dimensional shift, 9 reversal. For each stage, the number of trials required to attain criterion for that stage is displayed.

**Matching to Sample Visual Search (M to S)**
Matching to Sample Visual Search is a speed/accuracy trade-off task, testing the subject's ability to match visual samples. An abstract pattern, composed of four colored elements is presented in the middle of the screen. After a brief delay, a varying number of similar patterns are shown in a circle of boxes around the edge of the screen. Only one of these matches the pattern in the center of the screen and the subject must indicate which it is by touching it. The score indicates the percentage of correct indications and the latency of the response.

**Rapid Visual Information Processing (RIVP)**
Rapid Visual Information Processing is a test of vigilance (sustained attention) with a small working memory component. A white box appears in the center of the computer screen, inside which digits, from 2 to 9 appear in a pseudo-random order, at the rate of 100
digits per min. Subjects are requested to detect consecutive odd or even sequences of digits and to register responses using the press-pad. Initially, the computer prompts the subject when sequences appear and gives feedback when the pad is pressed. As the practice part of the test progresses, these cues are gradually phased out, and in the assessment part no cues or feedback are given. The score is displayed in the probability of hit and the probability of false alarm. Further, the sensitivity i.e. how good the subject is at detecting target sequences is shown. The also displayed response bias is the tendency to respond regardless of whether the target sequence is present. A score close to 1 indicates that the subject gave few false alarms. The latter two measures are calculated by CANTAB following descriptions published earlier (Grier 1971).

Spatial Working Memory (SWM)
This self-ordered searching task assesses both accuracy of spatial working memory and strategic ability at the same time. The aim of the test is that the subject finds a blue ‘token’ in each of the boxes displayed and use them to fill up an empty column on the right hand side of the screen, whilst not returning to boxes where a blue token has previously been found. The color and position of the boxes used are changed from trial to discourage the use of stereotyped search strategies. Accuracy of spatial working memory is measured by the number of errors (returning to an ‘empty’ box in which already a token has been found. The strategy score indicates the ability of the subject to adopt a systematic searching approach.

Statistical analysis
Plasma levels of tryptophan and CANTAB results between patients and controls were compared using analysis of variance with Bonferroni post hoc tests used to determine the direction of significant effects (SPSS 10.0). Because there were group differences in age, in all analyses age was treated as an independent factor. Plasma tryptophan levels were correlated to 24 h urinary 5-HIAA using the Spearman rank test.
Table 1: Demographical, medication and biochemical data of patients.

<table>
<thead>
<tr>
<th>sex</th>
<th>age</th>
<th>medication</th>
<th>urinary 5-HIAA mmol/mg creat</th>
<th>plasma tryptophan mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>50</td>
<td>octreotide</td>
<td>28.8</td>
<td>31.7</td>
</tr>
<tr>
<td>M</td>
<td>59</td>
<td>octreotide</td>
<td>29.8</td>
<td>31.5</td>
</tr>
<tr>
<td>F</td>
<td>46</td>
<td>octreotide</td>
<td>105.5</td>
<td>38.0</td>
</tr>
<tr>
<td>F</td>
<td>75</td>
<td>octreotide</td>
<td>13.4</td>
<td>54.9</td>
</tr>
<tr>
<td>F</td>
<td>67</td>
<td>octreotide</td>
<td>2.0</td>
<td>39.2</td>
</tr>
<tr>
<td>M</td>
<td>55</td>
<td>octreotide</td>
<td>205</td>
<td>28.0</td>
</tr>
<tr>
<td>M</td>
<td>64</td>
<td>octreotide</td>
<td>28.3</td>
<td>26.5</td>
</tr>
<tr>
<td>M</td>
<td>65</td>
<td>octreotide</td>
<td>5.0</td>
<td>59.3</td>
</tr>
<tr>
<td>F</td>
<td>61</td>
<td>none</td>
<td>24.6</td>
<td>52.2</td>
</tr>
<tr>
<td>M</td>
<td>57</td>
<td>octreotide</td>
<td>174.5</td>
<td>29.2</td>
</tr>
<tr>
<td>M</td>
<td>57</td>
<td>none</td>
<td>21.2</td>
<td>49.0</td>
</tr>
<tr>
<td>F</td>
<td>57</td>
<td>octreotide</td>
<td>47.9</td>
<td>39.1</td>
</tr>
<tr>
<td>F</td>
<td>71</td>
<td>octreotide</td>
<td>13.6</td>
<td>59.2</td>
</tr>
<tr>
<td>M</td>
<td>55</td>
<td>octreotide</td>
<td>10.6</td>
<td>62.1</td>
</tr>
</tbody>
</table>
Results

Biochemical analysis
All participants exhibited platelet 5-HT content above reference values. Plasma tryptophan levels (mean 41.2 mmol/L, standard deviation 13.1) were lower compared to sex and age matched healthy controls (mean 56.7 mmol/L, standard deviation 9.3, F(1,26)= 4.42, p=0.045). Plasma levels of tryptophan were negatively correlated to 24h urinary 5-HIAA levels (F(1,26) =-7.67, p=0.001). No significant effect of age differences between the two groups were detected in any task except for the M to S visual search.

Neuropsychological tests (see table 2)
ID-ED shift
Remarkably, carcinoid patients needed on average less trials to complete the task than the reference control group (F(1,26) = 4.86, p= 0.037). This seemed due to superior compound discrimination. Furthermore, there were no group differences in the number of trials required on the reversal stages of the task. With respect to the critical ID and ED stages, we found trend-like evidence that carcinoid patients performed better on the ID stage, while there were no group differences at the ED stage of the task.

SWM
Total errors were compared between groups. There was an effect of group due to carcinoid patients making significantly less errors than the controls (F(1,26) = 5.13, p= 0.032). No group differences were present in the strategy scores, indicating that both groups used an equally efficient searching strategy.

M to S
The dependent variables used for analysis were percentage correct and mean latency (in ms). No differences were detected between correct percentages. However, carcinoid patients needed significantly more time to select the matching stimulus (F(1,26) = 6.91, p=0.014). Independent testing revealed a significant effect of age differences between the groups on this test (F(1,26) = 5.7, p = 0.026).

RVIP
Carcinoid patients displayed a decreased sensitivity in visual atten-
tion ($F(1,26) = 12.05, p = 0.002$) due to a decreased percentage of hits ($F = 10.03, p = 0.004$). Carcinoid patients used a more liberal criterion for deciding when the stimulus was a target ($F(1,26) = 8.29, p = 0.008$), however they did not make more false alarms than normal controls ($F(1,26) = 0.094, p = 0.76$).

**Table 2:** Neuropsychological test data of carcinoid patients and normal controls

<table>
<thead>
<tr>
<th>ID/ED shift</th>
<th>patients mean (SD)</th>
<th>controls mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage 1</td>
<td>7.00 (1.36)</td>
<td>7.79 (2.36)</td>
<td>0.29</td>
</tr>
<tr>
<td>stage 2</td>
<td>8.14 (2.63)</td>
<td>9.64 (3.88)</td>
<td>0.24</td>
</tr>
<tr>
<td>stage 3</td>
<td>7.79 (3.12)</td>
<td>14.64 (9.91)</td>
<td>0.021</td>
</tr>
<tr>
<td>stage 4</td>
<td>6.14 (0.53)</td>
<td>7.10 (1.69)</td>
<td>0.060</td>
</tr>
<tr>
<td>stage 5 reversal</td>
<td>8.79 (4.37)</td>
<td>10.64 (6.29)</td>
<td>0.37</td>
</tr>
<tr>
<td>stage 6 ID</td>
<td>6.36 (0.63)</td>
<td>7.36 (1.78)</td>
<td>0.058</td>
</tr>
<tr>
<td>stage 7 reversal</td>
<td>7.14 (0.36)</td>
<td>10.92 (7.04)</td>
<td>0.055</td>
</tr>
<tr>
<td>stage 8 ED</td>
<td>18.21 (10.31)</td>
<td>18.29 (8.75)</td>
<td>0.98</td>
</tr>
<tr>
<td>stage 9 reversal</td>
<td>9.14 (4.80)</td>
<td>8.79 (3.98)</td>
<td>0.83</td>
</tr>
<tr>
<td>all stages</td>
<td>79.14 (13.63)</td>
<td>92.64 (18.41)</td>
<td>0.037</td>
</tr>
<tr>
<td>% correct</td>
<td>97.77 (4.65)</td>
<td>96.26 (0.83)</td>
<td>0.24</td>
</tr>
<tr>
<td>latency (ms)</td>
<td>2482 (1158)</td>
<td>1632 (349)</td>
<td>0.014</td>
</tr>
<tr>
<td>probability hit</td>
<td>0.34 (0.16)</td>
<td>0.53 (0.17)</td>
<td>0.004</td>
</tr>
<tr>
<td>probability false</td>
<td>0.048 (0.073)</td>
<td>0.039 (0.078)</td>
<td>0.762</td>
</tr>
<tr>
<td>sensitivity</td>
<td>0.80 (0.071)</td>
<td>0.87 (0.036)</td>
<td>0.002</td>
</tr>
<tr>
<td>response bias</td>
<td>0.74 (0.24)</td>
<td>0.94 (0.04)</td>
<td>0.008</td>
</tr>
<tr>
<td>total errors</td>
<td>31.71 (20.73)</td>
<td>45.84 (10.72)</td>
<td>0.032</td>
</tr>
<tr>
<td>strategy score</td>
<td>35.00 (4.42)</td>
<td>35.92 (1.56)</td>
<td>0.47</td>
</tr>
</tbody>
</table>
Discussion

Biochemical analysis revealed that plasma tryptophan levels of our patient group was significantly lowered, which can be taken to reflect a reduced central 5-HT function (Young et al. 1985). The negative correlation between tumor endocrine activity and plasma tryptophan levels further indicates that 5-HT-ergic neurotransmission is disturbed in these patients due to decreased precursor availability. With respect to executive function, carcinoid patients needed significantly fewer trials to complete all stages of the ID/ED Task. This suggests that patients were overall faster than controls to learn what aspects of the stimuli were relevant for reinforcement. There was (trend-like) evidence that this enhanced ability was also present when patients had to generalize a previously learned discrimination to a novel set of exemplars from the same category (IDS), and when these discriminations were subsequently reversed. However, patients performed comparable to controls when they had to shift their attention to a previously irrelevant stimulus dimension (EDS). These data refer to a slightly superior ability of carcinoid patients to learn relatively easy discriminations. However, this advantage is no longer present when more demanding discriminations must be made. This enhanced learning in the early stages of the task suggests that carcinoid patients do not 'stick' very much to previously learned associations, and instead are very quick in acquiring new behavioral responses. It is possible that this bears some relation to the 'lability' of attentional set that was recently observed after tryptophan depletion in healthy volunteers (Rubinsztein et al. 2001). This is reminiscent of the report of Coull et al. 1995 in which tryptophan-depleted subjects were better able to suppress automatic visuo-motor response associations. It is also in line with the study of Schmitt et al. in which enhanced ability of tryptophan depleted volunteers in to suppress visuo-verbal response tendencies in the Stroop task was reported. Our data contrast with those observed in major depression, as these patients are specifically impaired on the EDS stage of the task, while performance in earlier stages are unimpaired (Beats et al. 1996; Purcell et al. 1997).

Our data reveal normal performance on the match to sample task. Though carcinoid patients took more time to react, this was found to
be related to age differences between patients and controls. This suggests that the carcinoid patients did not have particular problems in directing their visual attention and selecting the matching stimulus.

Significant impairments were found on the RVIP task, in that patients were less able than controls to detect target sequences from a long series of digits presented on the computer screen. This refers to a decreased sensitivity of sustained visual attention. In addition, carcinoid patients used a more liberal response bias, indicating that these patients said more easily ‘yes’ to a particular stimulus. However, this response tendency did not result in a significantly elevated number of false alarms on the task. The finding of impaired sustained attention in carcinoid patients seems difficult to interpret, as the ATD studies that we know of did not include measures of sustained attention in their test batteries. In a recent rat study, no effects of ATD were found on sustained attention (Blokland et al. 2002). In depressive patients, sustained attention was found to be impaired as measured by the Continuous Performance Test (Liu et al. 2002).

Finally, on the spatial working memory task, carcinoid patients made significantly fewer errors than normal controls, while they used an equally efficient strategy. This refers to a superior ability of carcinoid patients to hold visuospatial information ‘on line’ in short term memory while performing the task. These findings contrast with the lack of effect of tryptophan depletion on spatial working memory (Park et al. 1994) and normal performance of depressive patients on this task (Purcell et al. 1997). However, animal studies do provide evidence of improved working memory function in 5-HT depleted conditions (Fontana et al. 1995, Altman and Normile 1986). Administration of the 5-HT releasing agent fenfluramine was reported to impair spatial working memory processes of healthy volunteers (Luciana et al. 1998).

An issue that has to be addressed is the possible effect of medication on cognitive performance in the patient group. Most patients were on the somatostatin analogue octreotide. However, this compound is not likely to pass the blood-brain-barrier (Jaehde et al. 1994). In a recent study somatostatin was shown to improve memo-
ry function in Alzheimer patients. However, these effects were not seen in an age matched group of healthy controls. The authors link these effects of somatostatin to specific defects in insulin-mediated energy metabolism seen in Alzheimer disease. In our patient group, glucose levels were not abnormal. Taken together, the cognitive patterns we found in carcinoid patients are probably not caused by medication. Another issue is the possibility of secretion of neuroendocrine substances by the carcinoid tumor other than 5-HT. In this case the observed cognitive changes may not be specifically caused by 5-HT depletion. However, although some carcinoids do secrete small amounts of histamine and/or catecholamines, highly hydrophilic substances do not cross the blood brain barrier. Because they are secreted only in small amounts this will not interfere with precursor availability. This means that changes in cerebral neurotransmission in our patient group can be attributed to a specific 5-HT-ergic effect.

In conclusion, we found evidence for impaired sustained attention but superior discriminative learning and visuospatial span in patients suffering from midgut metastatic carcinoid. These cognitive features of carcinoid patients only partly mimic earlier findings in tryptophan depleted volunteers. One explanation for this is that long-lasting disturbances in the central serotonergic system are present in carcinoid patients, while acute tryptophan depletion accomplishes only transient changes. Furthermore, the profile of cognitive impairments in our patients does not resemble the one observed in depressive patients except for impaired sustained attention but this feature is highly unspecific. Further investigations should learn if studies in chronic tryptophan depleted subjects will lead to new insights into the role of 5-HT in the accomplishment of affective states. It will be useful to study carcinoid patients using tests that measure cognitive, behavioral and affective functions.
References

Altman HJ, Normile HJ (1986) Enhancement of the memory of a previously learned aversive habit following pre-test administration of a variety of serotonergic agonists in mice. Psychopharmacology 90: 24-27


