The hepatitis C virus (HCV) is a simple RNA-chain virus 9,000–10,000 base pairs long whose genome codes both structural and non-structural proteins. There are six HCV genotypes known and their distribution varies in the different regions of the world. Genotypes 1 and 2 predominate in Portugal [1] and calculations show that there are between 80,000 to 100,000 (0.8–1%) individuals with chronic HCV infection [2], while on a worldwide scale, 3% of the population would be affected by HCV [3]. In the USA alone, chronic infection by HCV is responsible for more than 8000 deaths annually and the US Centers for Disease Control and Prevention foresee that mortality related to HCV can double or triple by 2020 [4,5].

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Executive Functions in Chronic Hepatitis C Virus-Infected Patients

Funkcje wykonawcze u pacjentów z przewlekłym wirusowym zapaleniem wątroby typu C

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Abstract

Background. The neuropsychological implications of severe liver dysfunction have been widely discussed in recent neuropsychological literature. However, research has only just begun on the harmful effects of mild liver dysfunction on neurocognitive processes as well as the direct action of the hepatitis C virus (HCV) on the central nervous system.

Objectives. The purpose of this study was to investigate the possible existence of alterations in the executive functions of HCV patients.

Material and Methods. The executive functions were assessed by the administration of the two test batteries related to frontal lobe functioning: the Behavioral Assessment of the Dysexecutive Syndrome and the Wisconsin Card Sorting Test, to a group of HCV patients (n = 20) and a control group (n = 20).

Results. The obtained results suggest the presence of impaired capability to inhibit previous associations and to use feedback in order to correct behavior in the HCV group. Structured planning, conceptualization, organized search, attention supervision, and control in non-routine tasks and maintenance of a non-automatic response are other impaired aspects in these patients.

Conclusions. The results were not related to the degree of liver fibrosis, suggesting direct action of the hepatitis C virus on the brain (Adv Clin Exp Med 2008, 17, 1, 53–60).

Key words: Neuropsychological evaluation, prefrontal functions, Wisconsin Card Sorting Test, liver fibrosis, cognitive impairment, frontal lobe damage.

Streszczenie

Cel pracy. Ocena funkcji wykonawczych u pacjentów z WZW typu C.

Materiał i metody. Badanie przeprowadzono za pomocą dwóch testów analizujących czynność płata czołowego, w grupie chorych z WZW typu C (n = 20) i w grupie kontrolnej (n = 20).


Słowa kluczowe: ocena neuropsychologiczna, Wisconsin Card Sorting Test, włóknienie wątroby, upośledzenie poznawcze, uszkodzenie płata czołowego.

This study was performed with grants from CESPU, crl, and MEC (SEJ 2004-07445 Psic).
triple in the coming 10 to 20 years [4]. In fact, HCV constitutes the main cause of morbidity and mortality linked to liver dysfunction due to its incidence in the formation of fibrosis, cirrhosis, and hepatocellular carcinoma [5]. These data, linked to the lack of an efficient vaccine, provide a view of the dimension and importance this infection has.

On the other hand, several studies on HCV-infected subjects have demonstrated that patients show varied and unspecific symptoms related to their nervous and psychological functioning even in the absence of serious histological liver damage [5, 6]. However, the evaluation of these symptoms becomes quite a hard task as there are many observations which reflect the existence of a high pathology rate in the psychiatric and psychological domain [7–10]. Some authors even support the idea that some symptoms, such as fatigue, should not be connected to HCV infection [11]. In this context, depression, stigmatization, and life quality are all clearly related dimensions and seem to have no apparent relation with liver necroinflammation or fibrosis grade [12].

Meanwhile, there is evidence pointing to a recovery of perceptions of wellbeing after a well-administered antiviral therapy, which partly indicates that life quality is linked to the pathological process [13]. These data can also indicate the direct action and effect HCV has on the brain. This possibility was already pointed out by Forton et al. [14], who found, using proton magnetic-resonance spectroscopy (1H MRS), high levels of choline/creatinine in the basal ganglia and white matter in patients with histologically mild hepatitis C compared with healthy volunteers and patients with hepatitis B. As HCV patients did not have significant fibrosis or liver cirrhosis, these observations cannot be explained by the presence of hepatic encephalopathy or by drug abuse, a possibility which had already been discarded by the authors by the exclusion criteria.

Other studies also point to a direct action of HCV on the brain. Kramer et al. [15] used the evoked potential technique to analyze the latency time of the P300 wave. Their work assessed information processing speed, reaction time, and the attention paid to a stimulus in individuals with chronic HCV infection and with several levels of hepatic fibrosis and hepatitis biochemical activity. The study showed that in HCV infection there were mild but significant neurocognitive dysfunctions and that the abnormalities detected in the P300 wave were not related to the grade of histological or biochemical activity of hepatitis, severity of fatigue, or mental health impairment. In that line, Weissenborn et al. [16] pointed to the presence of attention-process dysfunctions such as vigilance and change of attention linked to high anxiety and depression levels as well as to a slowdown in EEG and a diminution in the N-acetyl-aspartate/creatinine relation in the brain cortex. As the subjects in the sample did not have a significant liver deficit, the authors attributed the observed deficit to the action of the virus and not to the presence of minimal hepatic encephalopathy. Reaffirming the idea of a direct action of HCV on the brain, Peixoto et al. [17] identified alterations in immediate audio-verbal attention, visual-spatial perception, and visual-constructive capacity in patients with chronic infection caused by HCV. These alterations were not related to liver fibrosis.

As it has already been seen, chronic infection by HCV seems to imply an effect on brain functioning. The study of these alterations continues to be a fundamental process for the understanding of HCV patients and their neurological reality. Only in this way can a more consensual neurocognitive profile of HCV infection be reached and efficient neuropsychological rehabilitation programs be approached in order to keep patients autonomous and with adaptive capacity.

The Executive Functions (EFs) are the ones contributing more to the achievement of these two characteristics. A brain able to integrate information and to release it in a directed and regulated way is fundamental for the adaptation of individuals to the problems of daily routine. Naturally we can think that the results obtained in some of the previous studies are already clear and unmistakable indicators of the existence of executive deficits. However, this affirmation would not be totally correct. Today it is known that performance in several neuropsychological tests such as the Stroop and the Trail Making Test does not always correlate with the true executive deficit shown by the individuals [18, 19]. Given the importance and the variety of the cognitive functions of the prefrontal cortex it is believed necessary to study those EFs, such as planning capabilities, that have a greater impact on the patients’ quality of life in the context of HCV infection. This was the objective of the current study: to know the distribution of the possible executive alterations in patients with HCV chronic infection without liver cirrhosis and to compare the results obtained from a control group of healthy persons.

**Material and Methods**

**Participants**

This study comprised an experimental and a healthy control group (Table 1). The experimen-
tal group was made up of 20 subjects with chronic infection with HCV for over a six-month period. The liver fibrosis grade was always under four, which excluded the presence of liver cirrhosis (Table 1). The control group (n = 20) was made up of regular blood donors, which reduces the possibility of any kind of liver deficit because of the regular analytic examinations. The exclusion criteria at the moment of the neuropsychological evaluation or with regard to the recent medical record were the presence of previous hepatic encephalopathy and the existence of other neurological pathologies, psychiatric or psychological disturbances, cardio-respiratory pathologies, renal failure, diabetes, HIV infection, and the use of drugs, benzodiazepines, barbiturates, antihistamines, or alcohol. The experimental and the control groups did not significantly differ in age ($t_{(38)} = 0.096, p = 0.924$), gender, or education level ($t_{(38)} = 0.278, p = 0.782$).

Neuropsychological Evaluation

The objective of the neuropsychological evaluation was to evaluate the different components of executive functioning in a short period of time. The characterization and measurement of EF is one of the greatest challenges for neuropsychologists, firstly due to the need to structure a situation in which the subject will show how and when he organizes himself and, secondly, the dynamics and complexity of the object of study by itself [20]. Therefore, the Behavioral Assessment of the Dysexecutive Syndrome (BADS) was adopted as the central element in the evaluation as well as a computer version of the Wisconsin Card Sorting Test (WCST). BADS was selected due to its ecological value and the possibility to identify the executive alterations selectively, i.e. if the subject shows any global alteration or just a specific type of executive disruption [21]. The WCST appears as an additional means to study the components of the executive functions, mainly the components of planning, maintaining a behavioral strategy, and behavior self-regulation in response to environmental contingencies.

Behavioral Assessment of the Dysexecutive Syndrome (BADS)

The authors of this instrument state that its construction was largely influenced by the working memory model of Baddeley [22] and the attention supervision system of Norman and Shallice [23, 21]. The battery is made up of six tests which somehow relate to daily-life activities [24]: the

<table>
<thead>
<tr>
<th>Characteristics (Charakterystyka)</th>
<th>Control group (Grupa kontrolna)</th>
<th>HCV (Grupa chorych na WZW typu C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Sex (male/female) (Płeć)</td>
<td>15/5</td>
<td>15/5</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>45 ± 10</td>
<td>44 ± 12</td>
</tr>
<tr>
<td>Education status (Wykształcenie)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>elementary school</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>high school</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>college/university</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Liver fibrosis grade (Stopień zwłóknienia wątroby)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>MMSE (mean ± SD)</td>
<td>28.95 ± 1.05</td>
<td>28.90 ± 1.07</td>
</tr>
</tbody>
</table>

Rule Shift Cards Test, Action Program Test, Key Search Test, Temporal Judgement Test, Zoo Map Test, and the Modified Six-Element Test.

In the rule Shift Cards Test the subject has to perform a task with cards following a specific rule and a second task with the same cards but a different rule. The final result is obtained by adding the errors made on the second task. The test allows evaluating the ability to change rules, i.e. maintenance of the current rule and inhibition of the response linked to the previous rule. It also evaluates the working memory, as the subjects have to remember the previous card to emit a correct answer in agreement with the rule to be used.

In the Action Program Test the subject faces a task with several materials to be manipulated in five steps in order to achieve the final objective. To do so, certain objects can be freely used, but others not. This test has proven to be a good way to verify how the subjects respond to a new problem by manipulating a great variety of materials [21]. This test has no time limit and the final result is obtained by taking the number of helps provided by the researcher from the number of correct steps.

In the Key Search Test the subject is asked to develop an effective search previous to a hypothetical task. The subject is asked to look for a lost key on a surface represented by a white square drawn on a piece of paper. This test evidences the
ability of the subject to plan an efficient action and it allows monitoring the performance. The total scoring is obtained after a complex analysis of the adopted strategy.

The Temporal Judgement Test is a cognitive estimation test par excellence [25]. The subject is asked to answer four questions. These questions do not have a specific answer, but a reasoned one. The overall result is obtained after scoring the answers within a reasonable time interval for each question.

In the Zoo Map Test the subject is asked to show how to visit a set of previously defined premises by drawing an itinerary on a zoo map. Some of the rules to be followed include starting at the entrance and finishing in a specific area and using the paths marked in white only once. This test allows evaluating the ability for spontaneous and structured planning. The overall result is independent of the sequence of visits, the number of errors, and the time used.

Finally, the Modified Six-Element Test consists of three tests (dictation, arithmetic, and object naming) with two sub-tasks each. The subject is asked to perform some of the six sub-tasks within ten minutes. The only rule is not to do two sub-tasks of the same task consecutively. According to the authors of the battery, the Six-Element Test has proven to be an excellent way to verify planning and organization ability, attention focusing through time, and it also allows behavior monitoring.

**The Wisconsin Card Sorting Test (WCST)**

The WCST is the most popular test to detect a prefrontal dysfunction. There are numerous studies which reflect the activation of the prefrontal structures when performing this test [26, 27]. In this case, a computer version of the WCST was used. The subject receives a message with information on whether the card pairing is correct or incorrect. Using this feedback, the subject will try to make the greatest number of pairs possible. In this test there are several data to be extracted. Its analysis was made in this case by using the number of criteria categories reached (from zero to six), the number of times the subject insists on pairing cards with an incorrect but previously correct criterion (perseverative error), and the number of times the subject is unable to maintain the correct response after having made five good pairings (criterion maintenance error). This test assesses the ability to plan, to perform an organized search, and to use feedback in order to change strategies and impulse modulation-inhibition [24].

**Procedure**

The neuropsychological evaluation was performed at the Gastroenterology Service in two Portuguese hospitals. The ethics commissions of the hospitals issued favorable reports related to the experimental design and informed consent had been granted by all the subjects to participate in the study. Before applying the executive function evaluation tests, all the subjects in the sample were submitted to the Mini Mental State Inventory (MMSI) [28] in order to control the presence of hepatic encephalopathy or other more severe neurocognitive disruptions. Only the subjects scoring more than 26 points (the cut-off figure for the Portuguese population) in the MMSI were included in the study.

**Statistical Analysis**

The statistical analysis was performed using the computing program SPSS for Windows version 15.0. In order to determine the differences in the performance of the tasks among the groups, Student’s $t$ test was used. Differences with $p < 0.05$ were considered significant.

**Results**

The results obtained by the groups in the different neuropsychological tests are shown in Table 2. By applying Student’s $t$ test for each dependent variable, it can be verified that the HCV group obtained significantly lower results on the Rule Shift Card, Action Program, Key Search, and Zoo Map tests as well as on the three scorings assessed in the WCST. However, the results obtained on the MMSI ($p = 0.882$) and on the temporal judgement and Modified Six-Element of the BADS test did not show significant differences between the two groups (Table 2). There were no differences in any of the tests among the HCV subjects depending on their treatment (ribavirin and interferon-alpha or no treatment, Table 3), on liver fibrosis grade (Table 4), or on the etiology of the infection.

**Discussion**

The current study has provided evidence of the existence of executive deficits in patients with chronic infection caused by the hepatitis C virus. These alterations occur in HCV subjects without cirrhosis and the deficit also does not seem to depend on the fibrosis grade shown by patients, contrary to statements by other researchers [12,
Therefore, these observations seem to show the existence of a possible direct action of HVC on the central nervous system, as supported by Forton et al. [6, 14], with a likely effect on some structures of the frontal lobe. One of the most frequently observed features in patients with damage to prefrontal structures is their difficulty to use the information provided by environmental signals (feedback) in order to regulate or modify their behavior [31]. This is shown by the Rule Shift Card Test. It is considered as a visual discrimination-restitution task in which the subjects have to change their behavior (response to the presented card) depending on the context (task-associated rule), which obliges them to inhibit a previously established association [32]. In this context, the Rule Shift Card Test allows detecting irregularities in the attention supervisory or modulation systems and in sustaining the information during the test. This observation seems to be in agreement with the results obtained by Weissenborn et al. [16] in which they observed alterations in an attention-supervisory process.

The Action Program Test requires the subjects to be able to manipulate a variety of materials in order to solve a non-routine problem [21], and its validity lies in the difficulty found by prefrontal patients to develop new plans or cognitive strategies in order to solve a problem. This test implies the action of the attention supervisory system [23], exciting or inhibiting the action representations which are normally activated by certain stimuli, avoiding the generation of routine actions such as the resolution of the test by inverting the tube in order to access the plug, for example. Our research shows that this attention supervisory process is affected in the HCV group as they showed less capacity to solve the problem posed. This can be observed in the fewer correct steps taken.

In the Key Search Test the HCV subjects showed weak performance, evidencing the difficulties found in planning efficient actions and monitoring their own performance, as the patients could look at the lines drawn to show the itinerary followed and arrive at the conclusion that their search had not been efficient. This poorly planned and inefficient search can be related to the attitude of the subjects, taking more risks even at the expense of an efficient answer [33].

Regarding the WCST, the results in the number of categories obtained suggest alterations in the Executive Functions in Chronic Hepatitis C Virus-Infected Patients.

### Table 2. Descriptive statistics and significant differences in the results obtained by the two groups in the Behavioral Assessment of the Dysexecutive Syndrome (BADS) and the Wisconsin Card Sorting Test (WCST)

<table>
<thead>
<tr>
<th>Tests (Testy)</th>
<th>Control group (Grupa kontrolna)</th>
<th>HCV (Grupa chorych na WZW typu C)</th>
<th>P-value (Istotność statystyczna)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rule shift cards</td>
<td>2.85 ± 1.63</td>
<td>5.45 ± 2.06</td>
<td>0.000</td>
</tr>
<tr>
<td>action program</td>
<td>4.70 ± 0.57</td>
<td>4.25 ± 0.78</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>key search</td>
<td>12.75 ± 1.80</td>
<td>10.95 ± 1.39</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>temporal judgement</td>
<td>3.55 ± 0.60</td>
<td>3.20 ± 0.61</td>
<td>n.s.</td>
</tr>
<tr>
<td>zoo map</td>
<td>11.50 ± 2.30</td>
<td>9.65 ± 1.66</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>modified six elements</td>
<td>3.75 ± 1.02</td>
<td>4 ± 0.72</td>
<td>n.s.</td>
</tr>
<tr>
<td>WCST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>categories achieved</td>
<td>4.95 ± 0.82</td>
<td>3.90 ± 1.02</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>perseverative errors</td>
<td>8.30 ± 3.35</td>
<td>15.10 ± 5.51</td>
<td>0.000</td>
</tr>
<tr>
<td>failure to maintain set</td>
<td>0.15 ± 0.36</td>
<td>1.0 ± 0.91</td>
<td>0.000</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of results in HCV patients with treatment (Interferon-alpha + rivavirin, n = 5) and without treatment (n = 15) in the Behavioral Assessment of the Dysexecutive Syndrome (BADS) and the Wisconsin Card Sorting Test (WCST) (Student’s t test)

<table>
<thead>
<tr>
<th>Tests (Testy)</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rule shift cards</td>
<td>−0.93507</td>
<td>0.36</td>
</tr>
<tr>
<td>action program</td>
<td>−0.48245</td>
<td>0.63</td>
</tr>
<tr>
<td>key search</td>
<td>1.019373</td>
<td>0.32</td>
</tr>
<tr>
<td>temporal judgement</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>zoo map</td>
<td>−0.84755</td>
<td>0.4</td>
</tr>
<tr>
<td>modified six elements</td>
<td>−1.46603</td>
<td>0.15</td>
</tr>
<tr>
<td>WCST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>categories achieved</td>
<td>−1.28624</td>
<td>0.21</td>
</tr>
<tr>
<td>perseverative errors</td>
<td>1.10084</td>
<td>0.28</td>
</tr>
<tr>
<td>failure to maintain set</td>
<td>0.591198</td>
<td>0.56</td>
</tr>
</tbody>
</table>
conceptualization, abstract reasoning, and organized search abilities in the HCV group [24]. The perseverative errors made by the HCV group reveal an inability to use feedback and to correct their behavior by the changing criterion. The perseveration errors were observed in any task requiring changes in response strategy, which proves the implication of the frontal lobe in behavior flexibility and certain impulsivity in the patients with frontal damage. This impulsivity, mainly related to the dorsolateral area [26, 27, 34, 35], can also be considered as a deficit of impulse control [36]. The third WCST scoring, the failure to maintain the criterion, suggests a difficulty in patients with hepatitis C to maintain a non-automatic response, a typical difficulty in patients with prefrontal damage.

The Temporal Judgement Test intends to answer two questions: on the one hand is what Guilford [37] called divergent thinking, the type of reasoning which does not have a single correct answer and in which subjects with frontal lobe damage show a deficit, and on the other hand, the test is also useful in assessing the time estimation deficit in patients with frontal damage. However, the lack of differences among the HCV and control groups in this test can be due to the fact that it is highly improbable that patients show all the symptoms characteristic of the frontal functions [38]. The same explanation can also clarify the lack of differences in the Modified Six-Element Test or the complexity of the test itself.

It has been observed that patients with chronic HCV infection show disruptions in the ability to inhibit previous associations and to use feedback to correct behavior. They also show problems with structured planning, conceptualization, abstract reasoning, organized search, attention supervision and control in non-routine tasks, and in maintaining a non-automatic response.

No relation has been found between the applied anti-viral therapy and performance in the neuropsychological tests, which contradicts previous observations pointing at certain improvement in cognitive functions after using interferon-alpha [13]. However, the low number of subjects in each of the groups calls for caution regarding this observation. The fact that the liver fibrosis grade is not reflected in the results of the neuropsychological tests also highlights and reinforces the possible brain activity of HCV.

On the other hand, the implication of the frontal lobe in some psychiatric pathologies is well known. In this sense, Fontana et al. [9] observed more psychiatric symptoms and emotional disruption in HCV patients than in the general population. Their work shows that 35% of HCV subjects suffer from such emotional disruptions as obsessive-compulsive symptoms, psychoticism, and depression, indicating that it is necessary to study the etiopathogenics of emotional disruptions. It is possible that HCV activity on the frontal lobe, as this study seems to reflect, can be the basis for such emotional disruptions.

In conclusion, the data resulting from this study...
point to the need for a systemic assessment of the executive functions in HCV patients in order to identify the difficulties in planning and organizational tasks. There also seems to be an benefit in the use of neuropsychological tests with high ecological validity such as the BADS because of the direct relationship between the results of the test and impairments in daily life. The final objective would be neurocognitive rehabilitation in both ambulatory patients and patients who must return to their lives after a hospital stay with those abilities which allow a person to function independently, with a specific purpose, with self-sufficient behavior, and in a satisfactory way, to paraphrase Lezack [38].

References


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