Dig Dis Sci (2017) 62:794–800
DOI 10.1007/s10620-016-4425-6

ORIGINAL ARTICLE

Hepatic Encephalopathy Is Associated with Persistent Learning Impairments Despite Adequate Medical Treatment: A Multicenter, International Study

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Received: 16 March 2016 / Accepted: 16 December 2016 / Published online: 30 December 2016

Abstract

Background Hepatic encephalopathy (HE) is considered reversible regarding mental status but may not be cognitively in single-center studies.

Aim To evaluate persistence of learning impairment in prior HE compared to those who never experienced HE (no-HE) in a multicenter study.

Methods A total of 174 outpatient cirrhotics from three centers (94 Virginia, 30 Ohio, and 50 Rome; 36 prior HE) underwent psychometric hepatic encephalopathy score (PHES) and inhibitory control (ICT) testing at baseline and then at least 7 days apart. ICT learning (change in 2nd half lures compared to 1st half) was compared between patient groups at both visits. Change in the PHES individual sub-tests and total score between visits was compared in both groups. US versus Italian trends were also analyzed.

Results HE patients had worse PHES and ICT results compared to no-HE patients at baseline. Significant improvement (1st half 7.1 vs. 2nd half 6.2, $p < 0.0001$) was observed in no-HE, but not in HE (1st half 7.9 vs. 2nd half 7.8, $p = 0.1$) at baseline. At retesting (median 20 days later), no-HE patients continued with significant learning (1st half 6.0 vs. 2nd half 5.4, $p < 0.0001$), while HE patients again did not improve (1st half 7.8 vs. 2nd half 6.9, $p = 0.37$). Between visits, no-HE patients improved significantly on four PHES sub-tests and overall score, while HE patients only improved on two sub-tests with similar overall PHES score. Trends were similar between US and Italian subjects.

Conclusion In this multicenter study, prior HE patients showed persistent significant learning impairment compared to those without prior HE, despite adequate medical therapy. This persistent change should increase efforts to reduce the first HE episode.

Keywords Cirrhosis · Lactulose · Rifaximin · Inhibitory control test · Psychometric hepatic encephalopathy score

Abbreviations

PHES	Psychometric hepatic encephalopathy score
ICT	Inhibitory control test
MMSE	Mini-mental status examination
DST	Digit symbol test
TMT-A	Trail making test A
TMT-B	Trail making test B
SDT	Serial dotting test
LTT	Line tracing test
HRQoL	Health-related quality of life
SBP	Spontaneous bacterial peritonitis

Portions of this work were presented as an oral abstract in 2014 Annual Liver Meeting in Boston.

Electronic supplementary material The online version of this article (doi:10.1007/s10620-016-4425-6) contains supplementary material, which is available to authorized users.

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Introduction

The Spectrum of Neurocognitive Impairment in Cirrhosis (SONIC) spans the range from normal cognitive function to minimal hepatic encephalopathy (MHE) and overt hepatic encephalopathy (OHE) [1]. Both MHE and OHE are considered to be fully reversible with treatment [2]. Overt hepatic encephalopathy (HE) is characterized by a rostrocaudal progression of symptoms from deficits in attentiveness that may progress to lethargy, asterixis, disorientation, agitation, stupor, and coma. While mental status changes in overt HE improve after treatment, there is some evidence that the metabolic insult associated with overt HE may lead to chronic neurological injury that is not readily reversible [3–5]. Cognitive issues, such as learning impairment, have been reported in patients with prior overt HE episodes from single-center studies, accompanied by pathological evidence of neuronal death [6–9]. However, multicenter confirmation using more than one testing methodology is lacking.

Since the advent of the MELD score, HE has been removed from transplant priority, but patients with prior OHE also have a higher risk of persistent neurological impairment after liver transplantation [3–5]. In addition, studies have shown that it may be possible to prevent the first OHE episodes in cirrhotics [10]. Therefore, a multicenter evaluation of the impact of prior controlled OHE on learning impairment may be needed to refine patient management strategies. Improvement on cognitive tests due to prior exposure to the test materials (practice effects or learning capacity) tends to be robust in healthy older adults [11, 12] and generally absent in patients with dementia [13–15]. Based on this literature of practice effects and test/retest assessments, we hypothesized that subjects with a prior history of HE would show less benefit from prior exposure to the test items, or less of a learning capacity, compared to those with liver disease and no prior HE history.

This multicenter study was conducted to test the hypothesis that cirrhotics with a previous episode of OHE demonstrate a persistent learning impairment even after the resolution of OHE and with normal mental status despite lactulose/rifaximin therapy in a multicenter setting using two different testing strategies.

Patients and Methods

This was a prospective study of cirrhotic patients in three centers (a) Virginia Commonwealth University, Richmond, USA, (b) Metrohealth Medical Center, Cleveland, USA, and (c) Sapienza University, Rome, Italy. We included patients with cirrhosis proven by biopsy, endoscopic or radiological evidence, who were able to give written informed consent, had a mini-mental status examination score (MMSE) >25, were not on psychoactive medications apart from stable antidepressants, and were able to perform the cognitive tests. We excluded patients who were not able to give consent, had an unclear diagnosis of cirrhosis, and were on psychoactive medications other than antidepressants. None of the patients were on the transplant list, were undergoing HCV eradication therapy, had TIPS in place or portal-systemic shunts; none of the patients were exposed to these psychometric tests within the last 3 months. All subjects were enrolled after written informed consent and underwent cognitive testing at the same sitting. Demographic information, level of education, severity of cirrhosis, and MELD score were entered. A detailed history was obtained on previous episodes of overt HE. Patients were qualified as having a positive history if a previous episode of overt HE (grade II or over based on the West Haven criteria) was documented by a hospitalization and they were currently adherent on lactulose and/or rifaximin.

Patients underwent testing using two validated modalities at *baseline* and *retesting* between 7 and 30 days apart without intervening change in liver disease severity based on prior studies [6–8]. We aimed to study (1) intra-visit learning: improvement in ICT lures at baseline and separately at the retesting visit and (2) inter-visit learning: improvement in individual PHES sub-tests, total score, and total ICT lures and targets at the retesting visit compared to the baseline visit.

Psychometric Tests

All patients underwent the psychometric hepatic encephalopathy score (PHES) [16, 17] a paper–pencil battery test, including number connection test-A/B (NCT-A/B: subjects "join the dots" between numbers or numbers and letters in a timed fashion), digit symbol test (DST: subjects need to pair numbers with special symbols correctly within 90s), line tracing test (LTT: subjects trace a line between two parallel lines, time required is noted; errors were not recorded at all sites), and serial dotting test (SDT: subjects need to dot the center of a group of blank circles). According to the local norms of each site (Italy, Cleveland, and Virginia), a score of ≤ -4SD was considered MHE by PHES. A high score on DST and low score on the rest indicate good performance. Different versions of these tests were given at baseline and retesting visits.

The computerized cognitive test used was inhibitory control test (ICT) [18], in which subjects had to respond to alternating presentations of X and Y on the screen (targets) and to inhibit response when they did not alternate (lures). Outcomes noted were number of lures responded to; the 1st half of ICT is identical to the 2nd half, and therefore,

Table 1 Clinical and demographic characteristics, prevalence of previous overt HE, and cognitive tests in the patients included in the study

Age	Virginia ($n = 94$)	Rome ($n = 50$)	Ohio ($n = 30$)
Age (years)	56 ± 6	65 ± 10†	58 ± 9
Education (years)	13 ± 2	10 ± 5†	13 ± 3
Prior HE (%)	24 (26%)	9 (18%)	3 (10%)
MELD score	11 ± 6	11 ± 3	10 ± 4
History of ascites (%)	29 (31%)	21 (42%)	6 (20%)
History of variceal bleeding (%)	12 (13%)	13 (26%)	4 (13%)
On SBP prophylaxis (%)	4 (4%)	5 (10%)	0 (0%)
On non-selective beta blockers (%)	28 (30%)	20 (40%)	9 (30%)
Baseline PHES			
NCT-A (s)	38.6 ± 18.4*	57.2 ± 20.4	43.0 ± 19.0
NCT-B (s)	108.6 ± 71.4*	112.1 ± 44.6	114.2 ± 42.6
DST (score)	42.5 ± 14.5*	25.7 ± 9.4	37.6 ± 10.1
Serial dotting (s)	69.5 ± 35.2*	63.4 ± 19.1	93.3 ± 28.9
LTT time (s)	108 ± 49*	96.9 ± 81.4	119.3 ± 38.8
Total SD number on PHES	−3.8 ± 4.3	−2.1 ± 2.7	−3.2 ± 3.3
MHE based on PHES (%)	39 (41%)	12 (24%)	11 (37%)
Baseline ICT			
Total ICT lures (no.)	8.9 ± 7.1*	22.4 ± 10.1	13.5 ± 8.7
Total ICT targets (%)	94.6 ± 12*	87.2 ± 12.3	91.4 ± 12.6

SBP spontaneous bacterial peritonitis

* $p < 0.05$ between Virginia and other patients

† $p < 0.05$ between Rome and other patients

subjects with intact learning ability should improve (have less lures) in the 2nd compared to the 1st half at baseline as well as in the retesting visit.

These tests are used to diagnose MHE when they are impaired compared to the local population; however, we used each test result individually as well, since cognition is a continuum. Both the above techniques have been validated for evaluation of cognitive dysfunction in cirrhotic patients across several studies [16].

Statistical Analysis and Sample Size Analysis

Comparisons among groups were performed by analysis of variance (ANOVA), unpaired Student's t test, or Chi-square as appropriate intra-visit learning was studied using ICT lures (change in 2nd half lures compared to 1st half), which were compared between HE and no-HE patients at baseline and at the retesting visits.

A paired t test was used to compare changes in the PHES individual sub-tests, total PHES SD, and ICT lures and targets between baseline and retesting visits in HE and no-HE patients to analyze the inter-visit learning.

A p value of $p < 0.05$ was considered significant, and all data are displayed as mean ± standard deviation unless otherwise noted.

Sample Size

Primary endpoint was equivalence of PHES score for HE patients when comparing baseline and retesting measurements. Assuming a standard deviation of the difference of 1.25, an equivalence margin of 0.75, and a type I error rate of 5%, we calculated that a sample size of 35 patients would guarantee a power of at least 95%. Therefore, a lack of significance at 5% level in the comparison of PHES at baseline and retesting can be interpreted as evidence that the score has not changed.

Results

A total of 174 patients were enrolled of which 94 were from Virginia, 30 from Ohio, and 50 from Rome (Table 1). Demographics and cirrhosis severity characteristics were similar between sites apart from lower education and higher age in Italian patients. Thirty-six patients had prior HE (prior HE patients); these patients were controlled on lactulose and nine were on additional rifaximin, due to a more severe HE. The definition of treated HE was based on the disappearance of clinical findings. Half of the patients with HE had one prior HE episode ($n = 18$), while the remaining had experienced two ($n = 9$), three ($n = 5$), or

more ($n = 4$) episodes. The last HE episode was a median 5 (IQR 3–11) months prior to the study. Leading precipitating factors were dehydration and electrolyte imbalances ($n = 15$), infections ($n = 10$), constipation ($n = 5$), GI bleeding ($n = 3$) or were unidentified ($n = 3$), and in some cases, the correction of precipitating factors determined the resolution of HE without specific treatments. Analyzing the data of the patients with history of HE, 3 patients had grade IV HE, 6 patients grade III HE, and the remaining 27 had grade II HE. All HE patients were completely alert and oriented at the time of the testing (mini-mental examination score > 25). Not surprisingly, HE patients had a higher MELD score (16 vs. 10, $p < 0.0001$), greater proportion with prior variceal bleed (32 vs. 12%, $p = 0.006$), ascites (75 vs. 20%, $p < 0.0001$), being on SBP prophylaxis (19 vs. 1%, $p < 0.0001$), and non-selective beta blockers (49 vs. 29%, $p = 0.05$) compared to no-HE patients.

As a whole, performance on both paper–pencil and computerized tests was best in the subjects from Virginia, although the proportion with abnormal PHES remained same between sites (Table 1). As expected, HE patients had worse performance on all tests and had a higher proportion with abnormal PHES (MHE by PHES; 79 vs. 28%, $p < 0.0001$] compared to no-HE patients. There were no differences in the overall cognitive performance of subjects with >grade III HE in the past compared to others or in those with infection versus other precipitating factors among the HE patients ($p > 0.05$ for all comparisons).

All patients were retested a median of 20 days later (IQR 8–25 days) without change in cirrhosis severity, medications, or complications. There was no significant change in the MELD score (10.9 ± 4.9 vs. 10.4 ± 5.4, $p = 0.7$) and MMSE (28.6 ± 1.2 vs. 28.8 ± 1.5, $p = 0.1$) at baseline or retesting. Regardless HE, there were no differences between patients retested early (after 8 days) or later (after 25 days).

Intra-visit learning: At baseline evaluation, in no-HE patients significant learning took place with regard to (1st half 7.1 vs. 2nd half 6.2, $p < 0.0001$) ICT lures, but not in HE patients (1st half 7.9 vs. 2nd half 7.8, $p = 0.1$). At the retesting visit, no-HE patients demonstrated significant learning, or reduction in lures (1st half 6.0 vs. 2nd half 5.4, $p < 0.0001$), while HE patients again did not show ICT learning (1st half 7.8 vs. 2nd half 6.9, $p = 0.37$) (Figs. 1, 2).

Inter-visit learning: Comparing psychometric performance of retesting visit to baseline, including PHES and total ICT values, no-HE patients showed improvement in 4 PHES sub-tests, overall PHES SD score, and ICT (Table 2), while HE patients had an improvement only in 2 PHES sub-tests without changes in ICT or overall PHES SD score (Table 3). Prior HE patients continued to have a higher proportion with overall abnormal PHES (MHE by PHES 72 vs. 25%, $p < 0.0001$) compared to no-HE subjects.

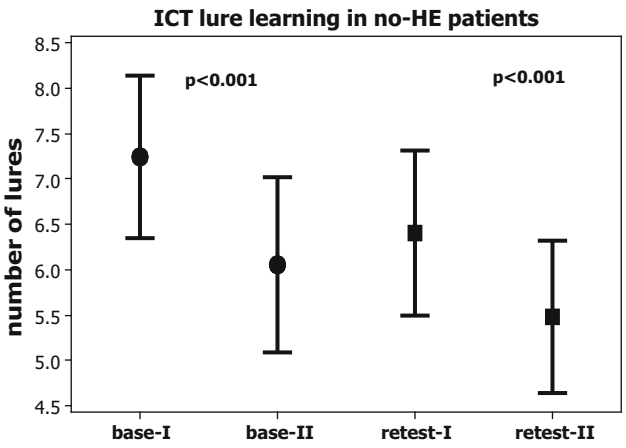

Fig. 1 Within-visit ICT lure learning in no-HE patients (mean, 95% CI). There was a significant improvement (reduction in ICT lures) in between the 1st and 2nd half (base I and base II) of the baseline visit and the retest visit (retest I and retest II)

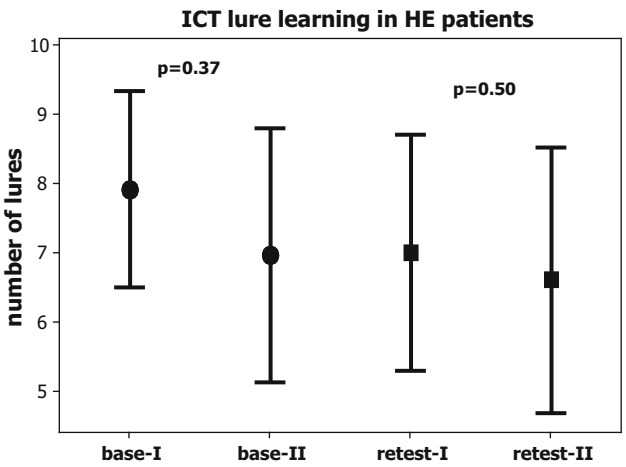

Fig. 2 Within-visit ICT lure learning in prior HE patients (mean, 95% CI). There was no significant improvement (reduction in ICT lures) in between the 1st and 2nd half (base I and base II) of the baseline visit or the retest visit (retest I and retest II)

An infectious versus non-infectious precipitating factor for the last HE episode did not impact ICT learning capability in the first visit (infectious 1st half 8.0 vs. 2nd 7.5, $p = 0.2$, non-infectious 7.5 vs. 7.4, $p = 0.13$) or second visit (infectious 1st half 8.1 vs. 2nd 7.7, $p = 0.42$, non-infectious 1st half 7.6 vs. 6.8, $p = 0.13$). The extent of PHES sub-test improvement was also similar between the groups with/without infectious precipitants. Similarly, there was no significant difference in the learning impairment in HE patients with one prior episode compared to those with >1 prior episode ($p = 0.3$ for lure learning visit 1, $p = 0.2$ for visit 2) regarding intra-visit learning and

Table 2 Retesting visit change in PHES and total ICT values compared to baseline in no-HE patients

No-HE patients ($n = 138$)	Baseline visit	Retesting visit	p value
MMSE (score)	28.5 ± 1.1	28.8 ± 1.3	**0.1**
NCT-A (s)	42.6 ± 14.8	36.2 ± 15.4	**0.05**
NCT-B (s)	103.3 ± 48.2	93.4 ± 51.4	**0.007**
DST (score)	46.1 ± 21.1	49.0 ± 21.7	**0.002**
Serial dotting (s)	68.7 ± 23.3	64 ± 14.5	**0.05**
LTT time (s)	101 ± 38.4	98.5 ± 37.5	0.20
Total SD number on PHES	−2.8 ± 3.6	−1.2 ± 3.1	**<0.001**
Total ICT lures (no.)	13.3 ± 10.5	11.8 ± 9.5	**0.05**
Total ICT targets (%)	92.2 ± 9.2	96.3 ± 8.7	**0.05**

Comparisons that are statistically significant are depicted in bold

Table 3 Retesting visit change in PHES and total ICT values compared to baseline in prior HE patients

Prior HE patients ($n = 36$)	Baseline visit	Retesting visit	p value
MMSE (score)	28.5 ± 1.4	28.6 ± 2.0	0.60
NCT-A (s)	56.4 ± 29.3	47.4 ± 21.9	**0.01**
NCT-B (s)	146.0 ± 90.1	131.3 ± 83.7	0.34
DST (score)	37.7 ± 16.3	41.6 ± 16.9	**0.001**
Serial dotting (s)	92.6 ± 47.8	84.9 ± 37.6	0.1
LTT time (s)	131.8 ± 55.1	124.6 ± 71.5	0.4
Total SD number on PHES	−6.0 ± 4.9	−5.4 ± 4.6	0.1
Total ICT lures (no.)	14.8 ± 9.1	14.3 ± 10.9	0.74
Total ICT targets (%)	84.1 ± 20.7	87.8 ± 20.4	0.39

Comparisons that are statistically significant are depicted in bold

inter-visit learning. A similar lack of trend was seen with grade III or higher HE compared to those who had only reached grade II HE in the past ($p > 0.05$ for all comparisons).

The US patients were similar to the Italian patients with respect to this pattern (Supplementary Tables 2 and 3).

Discussion

Both minimal hepatic encephalopathy and overt hepatic encephalopathy are generally considered to be fully reversible with treatment [2]. This assumption has often led practitioners to ignore potential residual issues with cognition that could further impact health-related quality of life (HRQoL) and daily functioning. This is relevant because research shows that despite therapy, patients with prior HE have worse HRQoL [19, 20], which is also demonstrated by changes in brain reserve on brain MR spectroscopy, diffusion tensor imaging, and functional MRI [21, 22]. Although a substantial proportion of cirrhotic subjects are not transplant candidates, it is also relevant to note that the shadow of pre-transplant HE extends toward the post-transplant cognitive recovery [3]. However, all prior studies are single-center experiences using either computerized or paper–pencil tests. Therefore, the determinants of this residual impairment need to be confirmed in a multicenter study using several testing modalities.

Our study design determined both the intra-visit (1st half ICT vs. 2nd half ICT) and inter-visit learning (total ICT and PHES scores) differences between patients with or without prior HE. The within-visit results confirm the prior single-center study, in that patients with prior HE lose their learning capability for ICT lures compared to those without HE [6]. This could be due to a reduction in attention that impacts learning capability or due to fatigue. Fatigue is an important determinant of driving and HRQOL as well [23, 24]. Interestingly, this pattern of performance continued even at the next visit, where this learning impairment in prior HE patient was again observed in all cohorts.

The between-visit results showed that prior HE subjects had difficulty in improving performance on tests apart from the NCT-A and DST. This translated into a similar performance on the other PHES sub-tests, the total PHES SD score and MHE rate, and the ICT lures and targets. This indicates a more generalized learning disorder in prior HE, since no-HE performance improved on almost all of the cognitive tests. The finding that the DST was one of the

measures sensitive to the anticipated learning effect across all study patients is not due to limited test–retest reliability [25], which remains excellent. Furthermore, it is not surprising that the DST and NCT-A continued to show the anticipated practice, or learning effects, across all study subjects. In a study clarifying cognitive domains sensitive to learning, or practice effects, Versavel et al. [26] found measures of attention/concentration and simple motor coordination most sensitive to practice effects. Only small practice effects were observed with measures of complex reaction and short-term memory. Therefore in our study, improvement in these specific tests in all patients could indicate a greater capacity for learning these simpler tasks compared to the more complex ICT, NCT-B, and LTT.

The between-visit results confirm single-center studies in Italy and India and extend it on to a multicenter context using two separate modes of testing, paper–pencil and computerized, as recommended by the EASL–AASLD guidelines [7, 8, 16]. Two potential components are thought to account for the learning ability: first, an increasing familiarity with performing tasks similar to specific tests (method variance); or being given any tests in general. A second factor may be due to specific item content familiarity over repeated presentations. To account for this potential confound we used, for a majority of the tests administered, alternate test forms. Despite use of alternate test forms, and controlling for test familiarity, no-HE patients significantly improved their cognitive performance, which has been referred to as the "test sophistication effect" [27]. This sophistication or learning effect was lacking in prior HE patients across intra- and inter-visit analyses.

This mirrors prior studies in other neurological diseases such as dementia in which this capability to learn is lost, unlike in healthy older adults [11–15]. This lack of learning also has prognostic value in groups with mild cognitive impairment and those who do not improve with retesting tend to have worse outcomes than those that do show improvements on retesting [28–30].

The heterogeneity of the three groups is strength of this study given that patients from several practices still had similar issues despite the differing therapies. This multicenter experience demonstrates that despite differences in the population demographics between groups, Italian and US-based cohorts had a similar pattern of reduced learning after the development of overt HE. The pattern remained within the prior HE patients regardless of the number of prior HE episodes, prior HE severity, or infectious versus other precipitating factors. This is similar to a recent multicenter study that showed that increased risk from HE from a pre-transplant listing standpoint remains independent of number of episodes and severity of the prior HE [31]. These findings demonstrate that development of HE itself may be sufficient to reduce learning. Further studies are needed using a larger HE sample to confirm these findings.

The mechanism for this change is not clear, although recent studies have demonstrated the activation of "senescence" genes in animal models of HE [32]. In humans, the brain MR evidence shows worsened brain reserve in prior HE subjects and on autopsy studies demonstrate astrocytosis [33]. There is also accumulating evidence, suggesting that the metabolic derangement caused by toxins other than ammonia, such as accumulation of manganese, mercaptans, or inflammatory cytokines, may result in neurological injury that can be persistent and possibly permanent [34–36]. The mechanisms behind the lack of reversibility of the neurocognitive status despite resolution of mental status changes need to be further understood.

The residual cognitive deficits in prior HE patients raise several clinically relevant questions. This should encourage research into prevention of the first episode of HE in a randomized double-blind placebo-controlled manner in a multicenter context. The worsened post-transplant cognitive course of these subjects should also spur research into improvement of priority of HE patients for liver transplantation.

In conclusion, this study has demonstrated in an international cohort of cirrhotic subjects the persistence of learning impairment within visits and between visits using computerized and paper–pencil modalities despite complete resolution of OHE with treatment and regaining normal mental status. Further research into the prevention of the first HE episode and streamlining HE into liver transplant priority is needed.

Funding This work was partly supported by NIDDK Grant RO1DK089713 awarded to JSB.

Author's contribution JSB, OR, and KDM were involved in the conceptualization of the project; SN, SA, RP, SG, AU, MB, EA, and ACF were responsible for recruitment and analysis of results; and SN, OR, AF, JBW, KDM, and JSB drafted the manuscript and were responsible for critical revisions.

Compliance with ethical standards

Conflict of interest The authors declare that no conflict of interest exists concerning this paper.

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