

Case Report

Identifying *Cryptococcus Neoformans* Neuroinfection Through Neuropsychological Examination

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Abstract: *Cryptococcus neoformans* is a highly lethal and hard-to-be-identified fungal disorder, being its neurocognitive impairment practically non-documented in literature. In this experience-based report, integrated analysis of symptomatology, history of life and neurocognitive assessment regarding a clinical case, provided a quick and easy-access identification of *cryptococcus neoformans* in a 77-year male (right-handed, 12 years of education). A semi-structured interview explored a variety of risk, favorable and influential factors. Neuropsychological battery included MMSE-2, Digit-Span, STROOP, RAVLT, COWAT, and Clock-Drawing Test. Quantitative and qualitative (verbalizations, test execution procedures and attitude) results have been integrated for his neuropsychological characterization. Main impairment occurred in semantics (mental confusion), processing speed and self-regulatory executive functions. Together, these cognitive functions rely on integrity of cortico-subcortical circuits. His verbal episodic memory was null, but this absent condition might be at least partially attributed to history of alcohol abuse. Motor disturbance slightly affected visuospatial praxia. Recommendations to identify rare neuroinfection through a neuropsychological approach include, beyond quantitative test results of a discriminant neurocognitive battery, proper identification of: an episode-related pattern of symptom evolution; a neurocognitive profile which resembles symptom evolution; and qualitative measures of transitory impairment. Thus, the proposed neuropsychological assessment approach is expected to fasten neuroinfection diagnosis and burn lethal possibilities, in simplified, yet fidedign and specialized, clinical contexts.

Keywords: *Cryptococcus*, Neuroinfection, Neuropsychological Assessment, Differential Diagnosis

1. Introduction

A lethal and hard-to-be diagnosed neuroinfection might be promptly identified through a low-cost non-invasive ambulatorial examination. This is the case of *Cryptococcus neoformans* meningitis (CM), and the experience of Charles (fictional name), a 77 years-old active male, examined by the author.

Cryptococcus is a non-contagious bird-transmitted fungus, which accesses brain through respiratory system and can promote dysfunction in circulatory systems in general, including blood and cerebrospinal fluid (CSF) systems. In neurologic system, it can promote inflammation response, ischemia and oxidative stress, seen in neuroimage as meningeal/gyral enhancement, basal ganglia

infarction/Virchow-Robin space dilatation, hydrocephalus and focal gray matter or white matter lesions [4, 16]. Delay on its diagnostic is, as high among HIV seronegative patients (65%), as lethal [17].

Its brain anatomical impact observed through magnetic ressonance is unspecific, requiring a more differential approach. Moreover, the analysis of its day-by-day symptomatology can be disguised by other confounding risk factors, present throughout someone's life experience. Scarce literature describes fluctuating consciousness, social isolation, memory complaints, personality changes; imbalance, psychomotor agitation, limb weakness; headache, fever, dizziness, visual and auditory hallucinations; and dependence for daily activities. [4, 5, 16].

Up to the moment, there are just 5 CM neuropsychological

clinical cases reported in literature. Clinical cases are highly informative regarding subtle but important differential approaches. For example, all of them highlight that CM can mimic other neurodegenerative irreversible conditions, like Alzheimer and vascular dementia; other neuroinflammation disorder, as neurosarcoidosis; as well as a neuropsychiatric disorder (psychosis), reaffirming their diagnosis challenge [1, 2, 8, 11, 13]. Thus, clinical reports increase validity of scientific communications to clinical contexts and strengthen clinicians to their daily professional challenges.

These clinical cases, in common with research studies, report mental confusion and lower scores in memory, language, perception, orientation, visuospatial praxia and abstraction [2, 4, 5].

Another peculiarity in literature about CM neuropsychological clinical cases is the lack of reports in a tropical country. In our country, Brazil, in an epidemiological analysis comprehended between 2000 and 2012, CM has been the 13th cause of death between chronic and recurrent infectious diseases [22].

In the present study, a comprehensive neurocognitive evaluation, with a differential diagnosis approach, was decisive in this clinical case, to rule out irreversible neurodegenerative conditions, consolidating the neuroinfection hypothesis. This immediate, brief and not discomforting clinical technique, while precise, is a highly-valuable resource, which attends clinical needs in different socioeconomic contexts.

The neurocognitive assessment conveys the administration of neuropsychological tests, sensible to brain damage. They evoke specific cognitive skills, like attention, memory and executive functions, providing reliable estimation of brain spare condition. In her almost 20-year clinical neuropsychological practice, integrated with research productions, the author has developed an integrative approach in her neuropsychological practice [18], incorporating to the interpretation of numerical results, the analysis of verbalizations, attitudinal and execution aspects – factors which also inform about cognitive subprocesses. Plus, these in-examination collected data are contrasted with daily functioning and symptomatology reports, reaching a coherent conclusion.

Hereby, Charles' neurocognitive analysis is expanded in order to reach a neuropsychological profile characterization of *Cryptococcus neoformans* meningitis, proposing a neuropsychological assessment approach, expected to fasten diagnosis and burn lethal possibilities, in simplified, yet fidedign and specialized, clinical contexts.

2. Materials and Methods

2.1. Patient Characteristics

Charles (fictional name) was a 77 years-old, right-handed male, with 12 years of education. Patient was alert, responsive and collaborative, despite reduced verbalization. Patient was able to do every basic daily life activity, needing support for

the instrumental ones. He previously lived in an urban city and, after retirement from his own business administration, moved to a rural zone. Charles lived with his wife and had been very active up to one year before, with no health issue nor continuous medicament use. He had presented previous history of alcohol abuse (3 or more shots daily), and 20 years ago reduced alcohol consumption frequency to weekend days, having totally stopped alcohol consumption 6 years before.

Regarding sensorial functioning, Charles had visual difficulties corrected by glass. He presented auditory difficulties, but would reject using hearing equipment. There were no signs of gustative or olfactory alterations. Charles presented sleep and eating alterations, with interrupted sleep and lack of appetite. He also presented significant weight loss in the last 5 months, having lost 33 pounds.

Charles had been exposed to chlorine inhalation for 2 year, while cleansing the pool, what was stopped one year before. He also presented history of tuberculosis, diagnosed 40 years before. Family history includes epilepsy and cancer.

His clinical course, with main symptoms, has been summarized in a timeline perspective, in Figure 2. His MMSE-2 score was 13. Illustrating his mental confusion, once he used the computer mouse assuming it was a phone and complained that his son wouldn't answer the phone. In another occasion, he woke up at night and wanted to urinate in the sink, also getting lost in his house's ambients.

After neuropsychological examination, his differential neurocognitive profile, suggesting neuroinfection, was communicated by the author to the spinal tap specialist, who later collected and analyzed CSF. Neuropsychological conclusion regarding neuroinfection, summed to uncommon reactions along the examination day (increased urinary incontinence, light fecal incontinence, and intense body trembling), motivated the laboratory to anticipate CSF results, confirming neuroinfection through *Cryptococcus neoformans*. Charles was submitted the same day to hospital internation for 47 days. According to his son, after hospital internation, the only cognitive complaint that persisted was recent amnesia. Patient recovered significantly from walking difficulties (short steps) and miccional emergency. However, still presented oral and motor hypotonia, not being able to stand for a long period, also still needing walking sticker.

2.2. Procedure and Instruments

A 77 years-old, active man was derived to neuropsychological examination, with a diagnostic hypothesis of normotensive hydrocephalus.

During anamnesis, Charles' son was main informant about patient's clinical and social history. A semi-structured interview explored a variety of risk, favorable and influential factors, including social support, family proximity, mood, cognitive and motor complaints, neuroimaging results, continuous medicament use and other health conditions. Emphasizing the importance of a historic approach, anamnesis was conducted in order to establish temporal relation between factors, relevant episodes and his functionality.

Neurocognitive examination comprised main measures of

classic neuropsychological tests. Forward and reverse Digit Span scores (WAIS-III) [23] were used to assess focused attention and working memory, respectively. Stroop – reading and inhibitory measures were used to evaluate speed processing and inhibitory control, respectively [7]. Comprehension, writing, naming, visuospatial praxia, were assessed with subscores from MMSE-2 [10]. Clock-Drawing Task (patient was asked to draw a clock indicating 10:15) total score was used for evaluating visuospatial praxia involving conceptual representation [20]. Episodic verbal memory was evaluated through RAVLT short-term retrieval (trial 6 score), long-term retrieval (trial 7 score) and discriminability of previously learned information (recognition score) [6]. Verbal categorization was measured through phonetic and semantic verbal fluency measures (COWAT) [9].

In addition, verbalizations, test execution aspects and attitudes presented during neuropsychological anamnesis and testing have been highly considered as qualitative results, when indicative of cognitive processing dysfunction.

All procedures were performed according to ethics guidelines from national Psychology board [19].

2.3. Statistical Analysis

Quantitative scores were adjusted according to normative data, achieving their z-score (standard-deviation). As commonly used, clinical criteria reclassified Charles' scores. Mild impairment was identified as $-1,5 \leq z\text{-score} \leq -1$. Moderate impairment was classified as $-2 < z\text{-score} < -1,5$. Severe impairment was determined by $z\text{-score} < -2$ [14]. Binary scores were identified as preserved or moderately impaired.

MMSE-2 score was decomposed according to assessed cognitive skills.

3. Results

Quantitative data has been collected from main measures in validated and classical neuropsychological tests. Qualitative data has been gathered from verbalizations, test execution procedures and attitudes. Figure 1 provides an integration of quantitative and qualitative results regarding neuropsychological assessment.

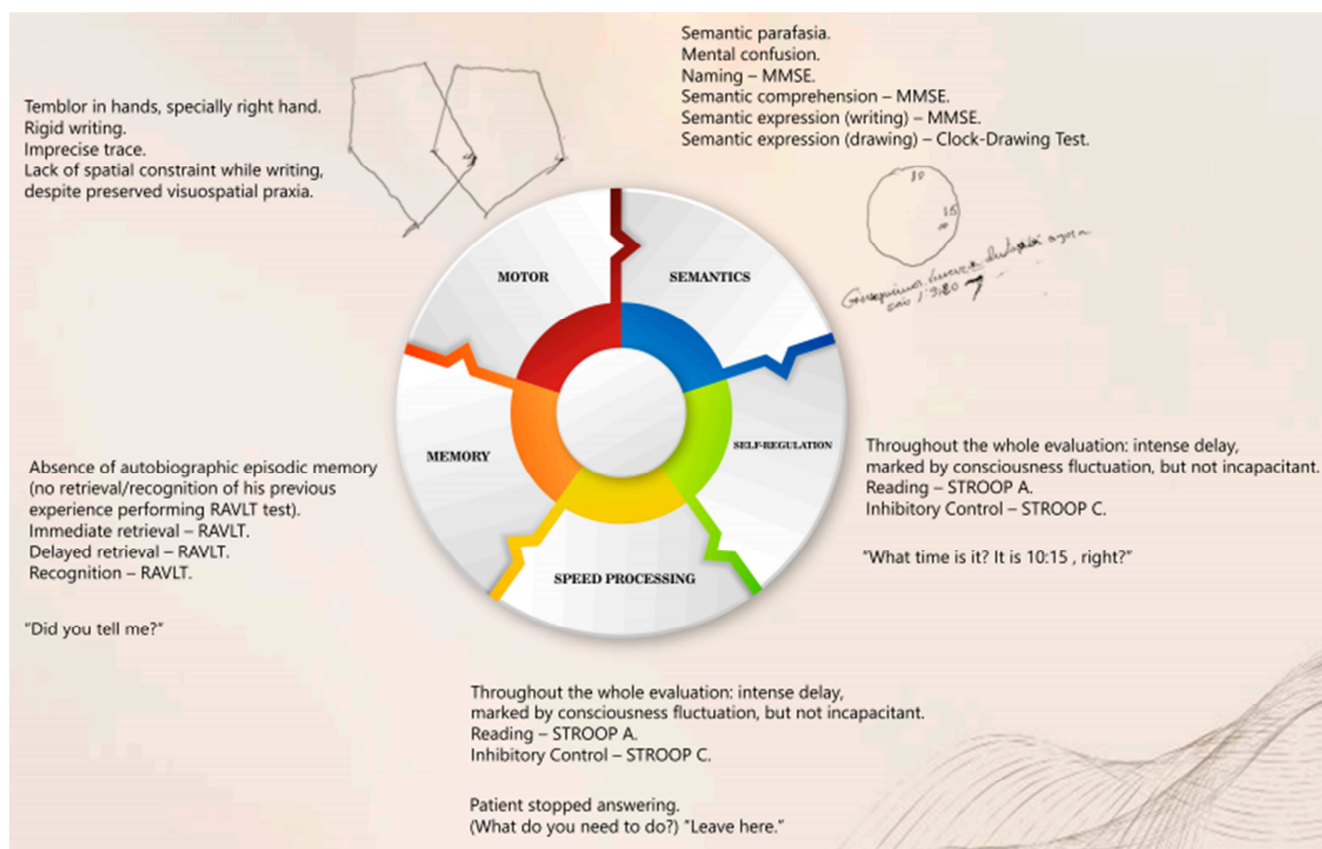


Figure 1. *Cryptococcus neoformans* neuropsychological profile: clinical case.

Charles has shown preserved dorsolateral frontal skills, namely, focused attention, working memory and phonetic verbal fluency. However, he presented mild dysfunction in semantic verbal fluency and repetition. Moderate impairment has been shown in some language features: semantic comprehension, semantic expression and denomination. Severe dysfunction has been shown in neurocognitive skills

more dependent on subcortical functioning: speed processing, inhibitory control and response supervision. Memory has shown to be null in immediate and delayed retrieval, mostly possibly related to his history of alcohol abuse (at least 2 to 3 shots/day, up to 20 years ago; followed by weekend consumption up to 2017), as reported in literature [21].

Figure 2 offers a history analysis of his symptoms and risk

factors. Then, this anamnesis analysis is combined with the neurocognitive analysis, in an attempt to reach a coherent and equivalent profile.

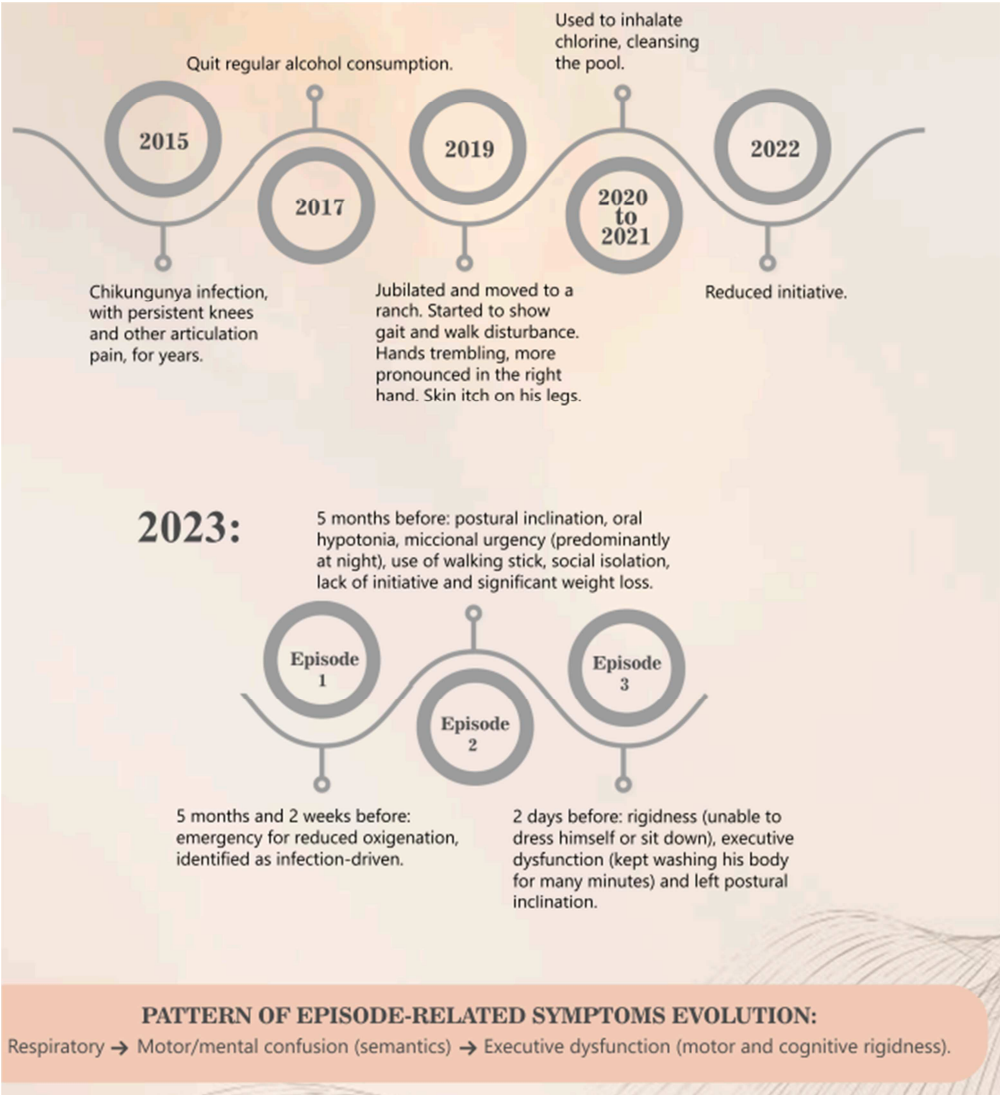


Figure 2. Symptoms timeline related to neuropsychological dysfunction level.

Moving forward, the differential neuropsychological approach that led to neuroinfection diagnosis has been summarized in Figure 3. Then, a cryptococcus neoformans meningitis discriminant neurocognitive assessment protocol has been suggested in Figure 4.

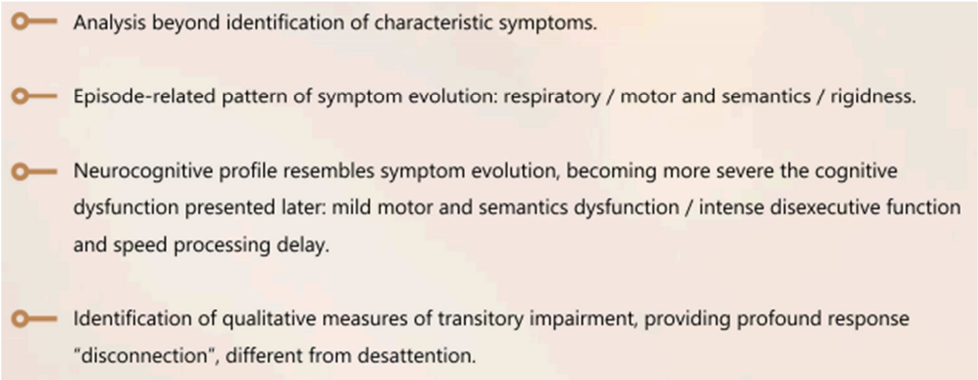


Figure 3. Differential neuropsychological assessment.

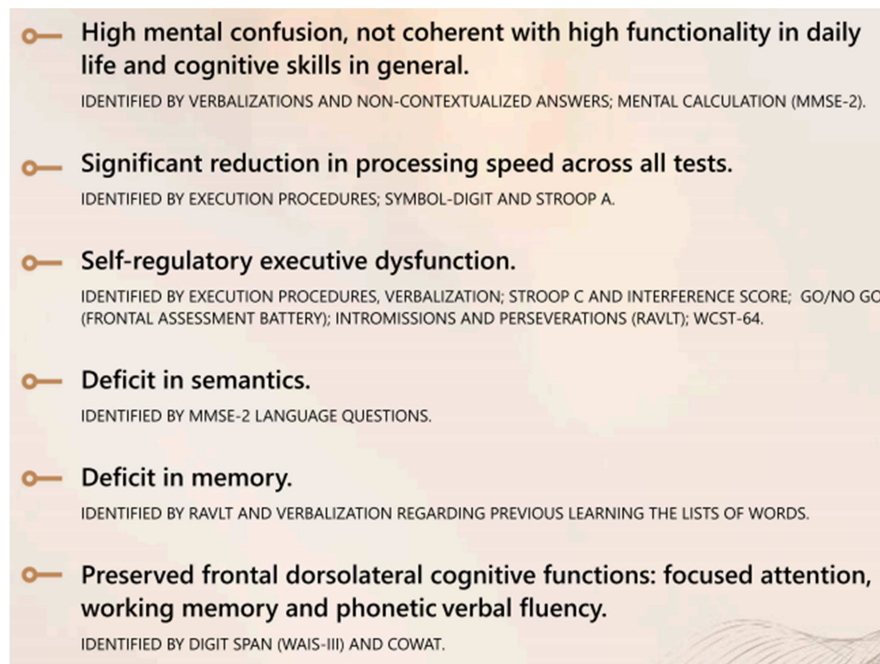


Figure 4. Discriminant neurocognitive profile.

4. Discussion

This is the very first scientific writing that offers clinical rationale to identify a neuroinflammation neurocognitive profile, later associated by external laboratory data to *cryptococcus neoformans* meningitis. Differentiating neurodegeneration from neuroinfection has not been well established in neuropsychological literature. Differently from what has been reported in CM neurocognitive literature, numeric results have been classified according to a clinical criteria and qualitative results elucidative of cognitive processing have been taken into account. Together, neurocognitive conclusions have been analyzed in conjunction with the detailed clinical history, achieved through comprehensive anamnesis. This clinical analysis approach emerged the identification of a coherent CM-related pattern of disease evolution, englobing daily functioning and neurocognitive activation, which led to proper neuroinfection diagnosis.

The most differential characteristic presented by Charles during neuropsychological investigation was lack of interoception sense, without any complaint regarding his life experience, despite observable motor and cognitive dysfunction. Interoception has long been neglected in neuropsychological protocols, but qualitative data, achieved through experienced clinical observation, highlights its importance for differential neuroinfection diagnosis.

Another remarkable aspect shown by Charles, both in anamnesis and in his responses to neuropsychological tests, was his transitory absence or lack of responsiveness. CM cases literature reports mental confusion, psychosis, or fluctuating consciousness [5, 13]. Being this sign a differential and highly informative cognitive processing index, its refined

characterization is demanded, in a way that formalized measures should be incorporated to neuropsychological protocols.

Differently from what has been reported in literature, Charles has shown preserved digit-span and working memory. This cognitive strength might be due to his educational level and professional history as an entrepreneur. Cases reported in literature had other manual occupations, like beef-cattle farmer or carpenter [5, 8].

Absence of abstract reasoning measure has been a limitation of this report, due to the increased execution time usually needed for tests regarding this cognitive function. However, in line with what is observed in Charles' other dorsolateral frontal cognitive functions (focused attention, working memory and phonetic categorization), abstraction is estimated to be preserved. Also, his difference from what is presented by CM research literature, reporting abstract reasoning reduction [3-5, 16], might be at least partially attributed to reduced validity of research differences in clinical context; or partially explained by his relatively high socioeducational background, as well.

Despite his preserved dorsolateral frontal cognitive functioning, Charles still presented a clear profile of semantic disorder, what might have underlied, at least partially, his mental confusion, as well the abstract dysfunction presented by other literature CM reported cases.

In CM, neurocognition seems to show progressive temporal-related level of dysfunction. This was observed in Charles' case and has been considered by Chen and colleagues' [3], indicating that better cognitive performances have been related to the stage of meningitis on admission [12, 15].

Charles' case is different than others reported in CM literature respect to his relatively recent migration to rural area, what has been shown in some cognitive differences. Then,

rural context shows to be relevant in a neurocognitive analysis not only due to increased neuroinfection risk, with more possibility of animals contact, but also due to differential neuroinfection cognitive impairment, in function of socioeconomic factors, like formal education and job skills. Thus, future studies and clinical practices might truly consider social history factors, as determinants for differential neurocognitive impairment, provoked by environmental exposure.

Also, Charles reported itch skin for some years, potentialized lately. Literature also reports itch skin in another HIV seronegative CM patient [5]. Thus, itch skin might be studied as a risk factor in HIV seronegative persons.

Charles' CM-related symptoms onset is hard to predict, considering other risk factors. However, in a posterior family interview, they reported that when moving to the ranch in 2019, they encountered plenty of sparrows and nest all over the ceiling. Their faeces would be commonly encountered on dinner table. These sparrows were there for almost one year, when they gradually started to cleanse areas. Also, in the cellar, there were plenty of bats and their faeces. Patient made himself responsible for cleaning up all these areas, without protection equipments or procedures. Thus, cryptococcus neoformans infection might have occurred in 2019, when some symptoms started to show up.

CM neurocognitive rehabilitation might focus on cognitive flexibility, semantics and speed processing. Time-limited and multiple-step tasks with language-related instructions convey an integrated cognitive practice for improving one's functionality in everyday life.

Brief, yet impactful, the proposed neuropsychological approach might be tested in other clinical contexts, in order to gather its diagnosing validation in a more expanded scenario. Specialized technicians, properly neuropsychologists, are crucial to refine individual conclusions in clinical diagnosis, respecting differential professional competences and classes.

Finally, a determinant factor for achieving Charles' neuropsychological conclusions was the examiner's presence in the present, beyond mindfulness, actively granting sense and coherence to the information all together.

Thus, this work proposes a discriminant neuropsychological protocol suggestion, based on a single clinical case, with its idiosyncratic factors. Further studies will clarify about its adequation informing about subtle brain functionality.

5. Conclusions

Differential contribution from this clinical report has been the primordial role of neuropsychological assessment to identify neuroinfection. Patient had been previously submitted to different neurologist and neuroimaging examinations, without a clear understanding regarding his progressive deterioration. Clinical interpretation in neuropsychology has shown in this ambulatory case to be a key factor changing directions in his treatment, and embasing an anticipation of laboratory results, which posteriorly detected cryptococcus

neoformans. Thus, comprehensive and integrated neurocognitive examination provides a refined understanding about brain functionality, showing to be crucial, highlighting rare and hard-to-be-identified health conditions.

Additionally, this work offers a solid CM differential neuropsychology battery, based on clinical experience. Clinical contexts in rural zone might benefit from this brief but yet accessible neuropsychology protocol suggestion, to further identify risks of CM neuroinfection through neurocognitive measures, forwarding patient directly to an infectology service, saving time and resources while reducing letal legacy from this fungus.

In few words, for a differential neurodegenerative – neuroinflammation approach, neuropsychological analysis should consider that temporarily dysfunctional cognitive performance during examination might be associated with pathologic agent. Null and incapacitating cognitive performance seems to be attributed to a prolonged, neurodegenerative condition.

Consolidated neuropsychological education is determinant and highly required for granting neurocognitive assessment the necessary clinical validation, in order to amplify individualized brain functioning comprehension and its benefits for one's life.

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Conflicts of Interest

The author declares no conflicts of interest.

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