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Schizophrenia vs. encephalitis: A neuropsychological case study

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ABSTRACT

From presenting with flu-like symptoms, seizures, and erratic behaviour including hallucinations, to being dismissed as “partying too much” and misdiagnosed with schizophrenia before the ultimate provision of a neurological explanation - encephalitis; this was a true sequence of events for the 24 year old female, Susannah Cahalan, who suddenly became ill with a mysterious illness that was misdiagnosed even after extensive evaluation until a neurologist was able to diagnose and effectively treat her (Cahalan, 2012; Barrett, 2016). Susannah's case bemused the medical field and became the plot of a book that subsequently garnered attention, large enough to be adapted into a movie, titled “Brain on Fire” (Barrett, 2016). Her case illustrated the exquisite interplay of neurology, physiology, and neuropsychology, complicated by personality traits and stereotypical behaviours observed in young adulthood, the period in which psychiatric illnesses also often begin to manifest. Unfortunately, while Susannah's case is rare, it is not unique. The following illustrates a case, similar to Susannah's, in which fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, chronological history, and neuropsychological test results supported a diagnosis of encephalitis, while symptom presentation, response to treatment, and neurological consultation, suggested a diagnosis of schizophrenia, demonstrating a significant overlap in presentation of these two disorders and the importance of a multidisciplinary approach to diagnosis and treatment (APA, 2013; Lancaster, 2016). This case illustrates the complexity of the art and science of diagnostics during the developmental period, reminding us as professionals of the importance of thoroughly reviewing a patient's medical history and of the vital contributions each discipline can make when attempting to diagnose and treat complex presentations.

From presenting with flu-like symptoms, seizures, and erratic behaviour including hallucinations, to being dismissed as “partying too much” and misdiagnosed with schizophrenia before the ultimate provision of a neurological explanation - encephalitis; this was a true sequence of events for the 24 year old female, Susannah Cahalan, who suddenly became ill with a mysterious illness that was misdiagnosed even after extensive evaluation until a neurologist was able to diagnose and effectively treat her (Cahalan, 2012; Barrett, 2016). Susannah's case bemused the medical field and became the plot of a book that subsequently garnered attention, large enough to be adapted into a movie, titled “Brain on Fire” (Barrett, 2016). Her case illustrated the exquisite interplay of neurology, physiology, and neuropsychology, complicated by personality traits and stereotypical behaviours observed in young adulthood, the period in which psychiatric illnesses also often begin to manifest. Unfortunately, while Susannah's case is rare, it is not unique. The following illustrates a case, similar to Susannah's, in which fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, chronological history, and neuropsychological test results indicated wide-spread brain dysfunction supported a diagnosis of encephalitis, while symptom presentation, response to treatment, and neurological consultation, suggested a diagnosis of schizophrenia, demonstrating a significant overlap in presentation of these two disorders and the importance of a multidisciplinary approach to diagnosis and treatment (American Psychiatric Association, 2013; Lancaster, 2016). This case illustrates the complexity of the art and science of diagnostics during the developmental period, reminding us as professionals of the importance of thoroughly reviewing a patient's medical history and of the vital contributions each discipline can make when attempting to diagnose and treat complex presentations.

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The patient’s initial psychiatric contact was as a 17 year old female presenting on March 7, 2018, with sudden loss of sleep, vomiting, withdrawal, refusal to attend school, irritability, confusion, emotional lability, flat affect, and preoccupation regarding her family’s safety. A full medical evaluation was completed and was unremarkable with the exception of lowered red and white blood cell counts and low alkaline, phosphorus, and magnesium. A Magnetic Resonance Image (MRI) of the brain was initially read as “normal,” but in light of the diagnostic possibility of anti-N-methyl D-aspartate (NMDA) receptor encephalitis, was re-interpreted as ‘subtle/questioning low increased T2 signal, which is fairly symmetric is present involving the mesial temporal lobe bilaterally. The appearance is nonspecific and may simply be within the broad range of normal, however limbic encephalitis, or recent seizure activity could result in this appearance.” Within three weeks of hospitalization, the patient rapidly deteriorated and went from responding slowly but in full sentences to no longer talking, walking, toiletting herself, or eating, requiring nasogastric intubation. Further medical investigations, including electroencephalogram (EEG) and lumbar puncture were within normal limits, although a metabolic consultation found a number of abnormalities in her amino acid assay and ceruloplasmin test.

A five day course of intravenous immunoglobulin (IVIG) and intravenous (IV) steroids was commenced, without improvement. The patient was initiated on electroconvulsive therapy (ECT), initially requiring higher doses of bilateral ECT parameters to achieve a short seizure event, with Flumazenil to reverse the high dose Ativan she had been receiving; ECT parameters were able to be reduced as patient began improving clinically. She demonstrated significant improvement with ECT; speaking and ambulating fluidly, but she continued to be psychotic and agitated.

An FDG-PET scan found “widespread pattern of abnormal metabolism with features suggesting subacute autoimmune encephalitis including intense symmetric hypermetabolism of the basal ganglia, bilateral occipital cortex hypometabolism, and hypometabolism of the medial frontal cortex bilaterally. Focal areas of hypermetabolism are demonstrated involving the mesial temporal cortices bilaterally matching areas of subtle signal abnormality on recent MRI. This is suggestive of limbic encephalitis. Overall hypermetabolism involves both cerebral hemispheres is right-sided predominant. Other regions of more focal hypermetabolism are seen involving the right lateral frontal cortex, right orbital frontal cortex, and right parietotemporal junction.” A four week treatment of rituximab was initiated for possible NMDA and seronegative autoimmune encephalitis. The patient demonstrated reduced paranoia, increased orientation, and improved hygiene after the first infusion and generally showed gradual improvements with some regression. However, treatment was confounded by ongoing ECT.

An EEG found “an excess pattern of slow theta activity involving the left temporal region, this may imply electrocortical dysfunction at the left temporal lobe, query sequelae of the possible underlying encephalopathic state. This is, in addition, a relative excess expression of fast beta activity, this may be seen in the context of exposure to neuroleptic agents, most commonly benzodiazepines.” A follow up EEG on May 16, 2018 indicated “an overall expression of slower theta, and at times even delta activity, that would go beyond that generally expected in this age group. In principle the effect of an encephalopathic state could account for the findings...” Electrolytic metabolic and encephalopathic etiologies may also account for such findings.” A repeat lumbar puncture was also completed, which found abnormal white blood cells, lymphocytosis, and elevation of glucose, however according to the Neurology consult these results could be explained by ECT.

Prior to discharge on June 14, 2018, after a total hospital stay of three months and 20 ECT treatments, the patient was stable for a couple of weeks, on no medications, and was reported to have returned to normal activities with no psychosis. A repeat brain MRI on August 14, 2018, stated that the “mesial temporal cortex is again noted to be thickened with increased T2 signal. There is involvement of the hippocampal gyri with extension more anteriorly in the mesial temporal cortex. The findings are unchanged from previous.” Over the next few months, it was noted that her academic performance had declined moderately (from the high 80’s to high 70’s) compared to her premorbid functioning and she obtained a Montreal-Cognitive Assessment (MoCA) score of 26/30 on November 22, 2018.

The patient remained stable and medication-free for nine months, but after a night of no sleep, the patient became agitated and restless, requiring hospitalization on March 13, 2019, and chemical/physical restraints; she was perplexed with a blank stare, and could not answer complex questions. 12 treatments of ECT were conducted and she was discharged from hospital on April 22, 2019, apparently at baseline on clozapine.

However, only days later she was readmitted after presenting to hospital disoriented, amnestic, disoriented, with disorganized speech, overvalued ideas, and hyperreflexia. Her MoCA score was 11/30. It was found that she had a repopulation of her CD19 and CD20 beta lymphocytes, which were previously suppressed by rituximab during the period of stability of almost one year, during which time there were no psychotic or mood symptoms despite no psychiatric medications. Full medical work-up was again completed, with attempts to minimize the confounds of psychiatric medication, which was not entirely possible due to ongoing agitation. Multiple investigations were conducted; cerebrospinal fluid (CSF) was normal, EEG was normal, MRI was unchanged with T2 signals. Another FDG-PET was completed on May 10, 2019, and read as an “abnormal pattern of moderate to intense patchy hypermetabolism in a distribution compatible with recurrent autoimmune encephalitis. Most marked hypermetabolism involves the basal ganglia bilaterally, lateral and orbitofrontal cortices bilaterally, precuneus and cuneus cortices bilaterally, small areas of the lateral posterior temporal cortices, and bilateral cerebellum. When compared to the previous PET/Computerized Tomography (CT) study, the distribution of hypermetabolism has changed to some degree. There has been interval resolution of previously noted mesial temporal hypermetabolism with an interval increase in bilateral frontal and parietal hypermetabolism. The distribution of hypermetabolism involving the cerebellum has also changed in the interval with more posterior medial involvement currently. The basal ganglia hypermetabolism and occipital cortical hypometabolism is similar. The overall distribution, intensity of cortical and basal ganglia hypermetabolism, intensity of occipital cortical hypometabolism, and interval change in distribution is not typical of classical psychiatric illness, favouring recurrent autoimmune encephalitis.” The patient was initiated again on IVIG and methylprednisolone IV; after one week, she was more organized, but continued to experience fluctuations, with episodes of paranoia, impostor syndrome, laughing/giggling/dancing for hours, alternating with episodes of tearfulness and behavioural regression. She was reintiated on rituximab and had an almost immediate response again, with slow but steady improvement.

Repeat PET/CT scans on June 6, 2019, indicated “Partial, but significant metabolic response to therapy with normalization of anterior to posterior gradient of cerebral cortical uptake, but mild residual bilateral frontal and parietal hypermetabolism, mild bilateral cerebellar hypermetabolism, and minimal right striatal hypermetabolism. The pattern would be most in keeping with interval improvement of autoimmune encephalitis, now in early recovery phase. Significant symmetric cerebral cortical hypometabolism including along anteromesial temporal lobes, bilateral perisylvian regions, and mesial frontal lobes is nonspecific, and is most likely at least in part related to medicaton effects, especially from concurrent corticosteroids, although chronic sequelia of previous injury (including infectious, inflammatory, and trauma), as well as superimposed negative spectrum psychiatric illness could have a similar appearance.” Her MoCA improved to 27/30 and affect was hyperthymic; she was described as being at her baseline.
and continued with maintenance IVIG and rituximab. The patient was discharged on July 5, 2019 after a total of ten weeks in hospital.

Another FDG-PET scan was completed approximately ten months later on April 21, 2020, as an outpatient; it demonstrated “partial improvement involving some previously noted hypermetabolic regions including the basal ganglia, thalami, frontal cortices, precuneus, and cuneus regions. The overall pattern of metabolism remains abnormal with persistent hypermetabolism of the frontal cortices bilaterally (sparring medially) and focal hypermetabolism of the posterior opercula bilaterally. As well new areas of abnormal hypermetabolism are demonstrated involving the lateral temporal cortices bilaterally. This may reflect partially treated autoimmune encephalitis. Treated autoimmune encephalitis revealing a background pattern of positive spectrum psychiatric illness could also potentially demonstrate this appearance. These are difficult to differentiate in this context.”

On July 17, 2020, the patient was brought to hospital with irritability, emotional lability, behavioural disorganization, and she was endorsing command auditory hallucinations; a brain MRI revealed “subtle symmetric Fluid-Attenuated Inversion Recovery (FLAIR)/T2 hyperintensity with associated thickening and expansion of the hippocampi is present on this study, unchanged compared to previous MRI. Remainder of the brain parenchyma is normal for signal and configuration. Normal caliber and contour of the ventricular system and basal cisterns.” The patient was discharged on August 11, 2020, on lithium, valproic acid, and olanzapine, with which she was noncompliant, resulting in repeated presentations to the Emergency Department for increasingly disorganized behaviour and thought processes, although some appeared to be purposeful in nature.

In the days prior to her current hospital admission which occurred on September 18, 2020, the patient had presented to the emergency department on five separate occasions beginning with abdominal pain, progressing to increased paranoia, bizarre and uncooperative behaviour, psychomotor restlessness, disorganized thought process, and violent behaviour. A neurology consult at the start of this hospitalization found no focal neurological deficits and in light of a recent full neurological evaluation with MRI, CSF, and EEG, which did not demonstrate any concerning abnormalities, the neurologist concluded that the FDG-PET scans in isolation were not objective evidence of encephalitis and given that the patient had two episodes of worsening on rituximab, was suggestive of a psychiatric illness.

After three weeks in hospital, psychology was consulted for a neuropsychological assessment on this now 19 year old female, which was hoped would assist with differential diagnosis. As can be seen from Table 1, the patient’s profile was inconsistent with her reported history of having been at least an average student, suggesting that the current cognitive profile actually represented a substantive decline from a previously higher level of functioning. Her profile demonstrated generally intact verbal, crystallized abilities, but significant impairments in memory, novel problem-solving, tasks of a visual-spatial nature, speeded tasks, or tasks requiring attention/concentration. Overall her performance was indicative of a significant deficit in her neuropsychological profile, involving both hemispheres, cortical and subcortical, with significant frontal system involvement.

The patient’s cognition was grossly more impaired than would be expected for a diagnosis of schizophrenia. While many clinicians still hold a neurodegenerative model of schizophrenia, more recent research and meta-analyses do not support the neurodegenerative model (Bora and Murray, 2014; Dickson et al., 2018). Rather, schizophrenia appears to be preceded by childhood dysfunction in multiple cognitive domains, representing widespread developmental deficits (i.e., impairments that emerge early and remain stable), including in verbal working memory, verbal functioning, scholastic achievement, and some executive function domains, particularly inhibition/switching (Dickson et al., 2018). The stability of cognitive functions in schizophrenia before and after onset of psychosis contradicts the idea that schizophrenia is a neurodegenerative illness, and rather lower IQ, persistent language

| Table 1 | Results of Neuropsychological Test Measures Administered to the Patient. |
|---------|--------------------------------------------------|
| ATT/CONC/PSPEED | Avg | Mild | Mod | Sev | T |
| Auditory attention | X | 53 |
| Auditory attention/working memory | X | 43 |
| Auditory attention/working memory | X | 37 |
| Auditory attention/working memory | X | 40 |
| Visual attention/working memory | X | 33 |
| Visual attention/working memory | X | 30 |
| Response speed | X | 76 |
| Concentration | X | 90 |
| Concentration | X | 41 |
| Visual scanning/processing speed | X | 53 |
| ATT/CONC/PSPEED | Processing speed | X | 38 |
| Processing speed | X | 22 |
| Processing speed | X | 34 |
| Processing speed | X | 38 |
| Verbal memory | X | 41 |
| Verbal memory | X | 37 |
| Verbal memory | X | 41 |
| Verbal memory | X | 24 |
| Verbal memory | X | 24 |
| Verbal recognition memory | X | 38 |
| Visual memory | X | 33 |
| Visual memory immediate | X | 47 |
| Visual memory delayed | X | 33 |
| Visual memory immediate | X | 33 |
| Visual memory delayed | X | 33 |
| IQ/premorbid | Reading (word decoding) | X | 51 |
| Reading comprehension | X | 43 |
| Expressive vocabulary | X | 50 |
| Crystallized intelligence | X | 33 |
| Visual abstraction | X | 30 |
| Visual-spatial Basic copy | X | 38 |
| Visual-spatial integration | X | <.20 |
| Visual-spatial integration | X | 27 |
| Executive | Executive function (errors) | X | 37 |
| Executive function (perseverations) | X | 39 |
| Executive function (categories) | X | 50 |
| Mental flexibility/processing speed | X | <.20 |
| Executive | Semantic fluency | X | 50 |
| Semantic fluency | X | 53 |
| Design fluency | X | 28 |
| Inhibition/processing speed | X | 33 |
| Motor/sensory | Grip strength, dom hand | X | 34 |
| Grip strength, nondom hand | X | 35 |
| Simultaneous stimulation, dom hand | X | 3/10 (raw) |
| Simultaneous stimulation, nondom hand | X | 4/10 (raw) |

Note. The specific names of the neuropsychological test measures have been omitted for the purpose of psychometric protection and were subsequently assigned generic names based on their measured cognitive domains.
impairment, and attention difficulties have been found to be key cognitive features associated with later psychosis (Bora and Murray, 2014; Poletti and Raballo, 2020).

The patient’s profile was more consistent with global insult/impairment from an encephalitis, most likely a recurrent autoimmune encephalitis, consistent with the repeat FDG-PET scans which demonstrated hypermetabolism in various locations, including the frontal and temporal cortices, in keeping with the various executive functioning and memory deficits found, whereas hypometabolism would be expected in schizophrenia (Moreno-Ajona et al., 2020; Newberg et al., 2011). Frontal and limbic dysfunction would also account for the emotional dysregulation that appeared to be a consistent part of her presentation.

The early (age 17), rapid, and abrupt onset of symptoms (preceded initially by vomiting only days earlier), the rapid fluctuations and variability observed in the patient’s mood, behaviour, and even in her cognition (her MoCA scores have ranged from 11/30 to 27/30), lack of family history of psychosis, results of the neuropsychological assessment and the thorough historical review are all supportive of a diagnosis of an autoimmune encephalitis. While she did have two instances of “worsening” symptoms/behaviours while on rituximab which, combined with ongoing diagnostic discord, resulted in its discontinuation, upon review of the patient’s history, most, if not all, of the “worsening” of symptoms appear to be emotional/behavioural in nature (e.g., panic attack, suicide attempt, running into traffic, outbursts of anger, etc.), as opposed to psychosis-related. While the patient has on occasion endorsed hallucinatory symptoms, she has never been witnessed to respond to internal stimuli and she has a tendency to over-endorse psychiatric symptoms which are typically non-substantiated upon further clarification.

This case clearly illustrates both the difficulty in diagnosing medical and psychiatric illnesses in the young adult population and the unique contributions that each discipline, including internal medicine, radiology, psychiatry, neurology, and psychology, can make in developing an accurate diagnostic picture. Thankfully, cases like this young female and Susannah’s remain relatively rare; unfortunately though, the sheer rareness contributes to the difficulty in arriving at an accurate diagnosis because there are other, simpler, and more frequent, explanations, highlighting the need to continue to advance the research and knowledge to reduce the number and impact of “Brain[s] on Fire.”

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