Obstacles to diagnostic investigation of a child with comorbid psychiatric conditions

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Abstract

Presented here is the unique case of diagnostic investigation for a 16 year old male presenting in an acute state of apparent psychosis. The patient had a long history of previous specialist work-ups, tentative diagnoses, multiple emergency department admissions, and medication trials, all of which failed to produce significant lasting relief. While initial encounters diagnostically centered on autoimmune encephalitis, comprehensive work-ups always drove the differential towards a likely psychiatric disorder. Despite this consistent professional opinion, tentative diagnosis of schizophrenia with underlying Autism Spectrum Disorder was delayed for many years, due to a variety of complicating factors. Overall, this case highlights many different considerations that might assist in avoiding a protracted road to diagnosis, including navigating the obstacles that parental interaction with a complex healthcare system can pose during diagnostic evaluation and recommended treatment as well as, the role of re-interpreting past test results within the context of new literature, and the complexities of diagnosing comorbid psychiatric conditions.

Keywords: autism spectrum disorder; schizophrenia; autoimmune encephalitis; chromosomal microduplication

Introduction

According to the Center for Disease Control's Autism and Developmental Disabilities Monitoring (ADDM) Network, an estimated 1 in 54 children have been diagnosed with Autism Spectrum Disorder (ASD) (1). The criteria used to identify such children is consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and includes such traits as “persistent deficits in social communication and social interaction across multiple contexts” as well as “the presence of restricted, repetitive patterns of behavior, interests, or activities” (2). Among the factors that may complicate the clinical picture of a child exhibiting such traits include the possibility of a comorbid psychiatric condition. Indeed, individuals with ASD are at greater risk of experiencing one or more co-occurring psychiatric conditions compared to the general population (3). Furthermore, the presence of a comorbid psychiatric condition can complicate the clinical picture of an individual's presentation with ASD through “symptom overlap, diagnostic overshadowing, and ambiguous symptom presentation in ASD” (3). A better understanding of how ASD co-presents with other psychiatric disorders can aid in more effective diagnostic approaches.

Just as individuals with ASD have a greater risk of having a co-morbid psychiatric condition, this increased risk extends specifically to co-occurring Schizophrenia Spectrum Disorders (SSD) (4). Conversely, children that demonstrate childhood-onset schizophrenia have been shown to be at greater risk for a history of premorbid ASD (5). These correlations provide evidence for a connection between these two psychiatric disorders, whether of a genetic, environmental, congenital, or other type of origin. However, this connection can pose challenges for diagnostic evaluation because these two diagnoses may be confused. This is at least partly owed to how the symptoms of one may be confused with those that are characteristic of the other, for example, 'idiosyncratic beliefs' in ASD vs delusions in psychosis (4). For this reason, it has been proposed, as by Cochran in 2013 (6), that "consideration of comorbid ASD and SSD should be given whenever there is a concern for psychotic
symptoms that are accompanied by a change from baseline presentation in individuals with ASDs.”

This case report seeks to illustrate additional factors that may further complicate the diagnostic evaluation of an individual found to have comorbid ASD and a psychotic psychiatric disorder, such as SSD. In particular, this report not only displays by example how such comorbid psychiatric conditions pose challenges for the identification of either condition, but also how characteristics of parental interaction with the healthcare system can further compound these challenges. Additionally, this case highlights the importance of re-interpreting the results of past diagnostic testing as a way to combat these challenges.

Case report
The patient was a 16-year-old male from an Orthodox Jewish community with past medical history significant for obstructive sleep apnea, developmental speech delay, and recurrent otitis media, who presented to the Emergency Department with a worsening altered mental status over two weeks in 2020. Per parents, patient had been exhibiting paranoid delusions, rigidity, ‘strange behaviors,’ and agitation that precipitated trying to run away from home. Mental Status Exam was significant for inattentiveness, flat affect, delayed speech, and thought content containing paranoid delusions. Patient was restless, agitated, and avoiding eye contact with evaluators. He additionally appeared distressed when describing the feeling of a ‘bug’ crawling on his back which he believed was a ‘parasite’ inside him. Parents denied a history of seizures, auditory or visual hallucinations, headaches, and there were no focal neurological deficits.

History gleaned from parents reported that patient had frequently experienced such described ‘episodes’ of a similar psychosis since age eleven. During the first occurrence in 2015, parents found the patient outside after returning home from school, in a state of confusion. He subsequently exhibited bizarre behaviors such as refusing to respond when addressed, unwilling to eat/drink secondary to fear of ‘contamination,’ paranoid delusions, and religious fixations. He was subsequently taken to the hospital and admitted for evaluation that involved a primary work-up for metabolic and autoimmune encephalopathies. In the interim, he received a combination of antipsychotic and benzodiazepine for sedation and control of psychotic symptoms. Patient improved over the course of a week, encephalopathies were ruled out, and the diagnostic focus shifted to primarily psychiatric etiologies. He received a diagnosis of Generalized Anxiety Disorder at the culmination of the first episode through evaluation by a psychiatrist by way of a consultation conducted during his stay, although it was not noted if this physician was a specialist in child and adolescent psychiatry.

Since that time in 2015, parents reported that about every four weeks the patient would become ‘difficult to manage’ or ‘out-of-control’ for about 5-7 days, with similar psychotic manifestations as the initial episode: religious fixations, limited speech, and obsessive-compulsive and paranoid tendencies surrounding food. During or directly following several such episodes, he was brought to the Emergency Department or outpatient office for evaluation, although no consistent identifiable triggers could be identified. Overall hospital course would remain similar with each encounter: receive antipsychotic and benzodiazepine medication, diagnostic evaluations to rule-out autoimmune or metabolic encephalopathies, then discharge with recommendation to further pursue psychiatric treatment. In each episode, the patient would be admitted under the neurological service, and it was unclear according to the available medical record how much, if at all, the patient was evaluated by the psychiatry service during each of his earlier admissions. Additionally, the available medical record did not demonstrate any occurrences of outpatient psychiatric evaluation, despite notes that this was often recommended upon discharges.

Beginning two years after the initial episode, parents stated that the patient intermittently displayed additional periods of apparent catatonia, where he would appear lethargic, low energy or ‘tired,’ be immobile, posturing, and lacking in spontaneous or responsive speech, with flat affect. Physician findings on physical exam of the patient in these states paralleled those reported by parents, while noting certain features classic of catatonia including echolalia and positive response to a lorazepam challenge.

At home, parents reported that patient would spontaneously return to ‘baseline’ in between episodes, without much help attributed to the variety of different treatments attempted over the years. During one documented encounter where parents were describing that the patient was exhibiting his ‘baseline’ behaviors, physician evaluation found him to be severely constricted, lacking spontaneous speech, with flat affect. Occasional incongruences were also noted between history provided by parents and documented medical records. In one example, the patient’s mother consistently stated that he had previously diagnosed autoimmune encephalitis, when this condition had been effectively ruled-out many times prior through extensive medical workups. She also stated that the patient had diagnosed Common Variable Immune Deficiency, when later a physician inquiry elicited that this was
the result of her own interpretation of a test that she had 'bought off of eBay.' Nonetheless, these diagnoses were documented and maintained over time through the medical record, apparently based only on these oral reports.

Over the years, this patient received evaluations by a growing list of different primary care providers and specialists at a minimum of six different major healthcare facilities. During hospitalization, while concurrently pursuing diagnostic work-up, patient would receive medication for both sedation and management of psychosis or catatonia. Treatments pursued through the years (in addition to the combination of antipsychotic with benzodiazepine, often used only ‘as needed’ due to parental discord on treatment regimen) included antibiotics, high dose corticosteroids, standing escitalopram, and intravenous immunoglobulin (IVIG). However, each of these treatments failed to yield long-term remission. Regarding IVIG: the patient received many rounds since disease onset and his response varied from improvement, to no change, to even worsening. Meanwhile, the combination antipsychotic and benzodiazepine regimen, frequently employed during initial patient encounters and during inpatient stays, consistently yielded at least partial improvement in his symptoms. However, due to documented parental preference against long-standing use of these medications, these drugs were consistently discontinued after discharge, despite many physicians recommending their use long-term for at least empirical purposes.

**Diagnostic focus and assessment**

During the initial work-up during hospital visits and admission, autoimmune encephalitis was usually at the top of the differential diagnosis list. Taking into account characteristics that included the reported ‘relapsing-remitting’ course, the abruptness of symptom onset, and the patient’s age, and reported history of immunologic pathophysiology (CVID, prior episodes of ‘confirmed’ autoimmune encephalitis) a comprehensive work-up for autoimmune encephalitis was conducted many times over the years without any significant findings. Initially, basic labs were always drawn including Complete Blood Count (CBC) with differential, Comprehensive Metabolic Panel (including Liver Function Tests), Urine Toxicology Screen, Serum Drug screen - these always yielded nonsignificant results. Thereafter, more diagnostically focused testing was conducted for auto-immune encephalitis (Table 1). Additionally, potential triggering pathogens were investigated with antibody or polymerase chain reaction (PCR) testing, within serum and/or cerebrospinal fluid (Table 1). Most of these tests were repeated several times over the course of years during repeat evaluations, each time universally yielding nonsignificant findings. With these nonsignificant findings, coupled with consistently negative comprehensive neurological exams for focal deficits, the differential diagnosis always shifted towards psychiatrically-focused diagnoses, after ruling-out other rarer medical etiologies.

More atypical etiologies that were frequently considered, and later ruled-out, included metabolic encephalopathies secondary to inborn-errors-of metabolism, including Wilson’s Disease and Acute Intermittent Porphyria. Clinical suspicion was often heightened by the classic association of many particular inborn-errors-of metabolism with this patient’s ethnic group (Ashkenazi Jewish). However, diagnostic testing for these conditions (Table 2), as with autoimmune encephalitis, always yielded results within normal limits, even when repeated several times over the years.

About two years after the start of these episodes and frequent medical encounters, this patient was referred for comprehensive genetic testing: Whole Exome Sequencing plus Whole Mitochondrial Genome Sequencing and SNP array. This testing found a microduplication on chromosome 15, at location 15q11.2, between Break Points (BP) 1 and 2 (also known as the ‘Burnside Butler Region’), comprising genes that include NIPA1, NIPA2, CYFIP1, and TUBGCP5. At that time, this finding was recorded as ‘likely benign’, and further genetic work-up of the patient or his parents was not recommended. However, a subsequent medical encounter cited that this finding was consistent with newer literature that correlated this microduplication with ASD. Nonetheless, subsequent medical encounters failed to explore this correlation and the possible applicability of ASD to this patient until the most current medical work-up. This trend was interesting to note when reviewing all previous medical encounter documents since psychiatric disorders were always reported as of high clinical suspicion in this patient after extensive work-up.

After the initial ‘episode’ at age eleven, this patient was formally diagnosed with Generalized Anxiety Disorder after consultation by a psychiatrist while inpatient and over the years of evaluations, this diagnosis stayed with him. However, other specific psychiatric conditions that were also considered included schizophrenia, ‘cycloid psychosis,’ schizoaffective disorder, and bipolar disorder. The last two were often of lower clinical suspicion due to the lack of clear affective symptoms. At the most current encounter, due to the long-standing history of positive responses to anti-psychotic regimens, and the overall clinical picture of periods of catatonia
with psychosis, the psychiatric diagnosis of highest clinical suspicion was schizophrenia. The DSM-V defines diagnostic criteria for schizophrenia as needing to have at least two of: 1. Delusions, 2. Hallucinations, 3. Disorganized Speech, 4. Grossly Disorganized/Catatonic Behavior, 5. Negative symptoms; with at least one of 1., 2., or 3. present (2). Additionally, these must be present for a significant portion of any 1-month period, with evidence of disturbed level of functioning for at least 6-months (2). The way in which details from the patient’s history of presentations during prior episodes, in addition to evaluation during the most current medical encounter, were correlated to meet these criteria is outlined in Table 3.
Additional features resembling ASD in the patient’s presentation during current and prior encounters, such as deficits in social-emotional reciprocity and nonverbal communication in the absence of psychotic symptoms once the current episode had subsided, as well as the specific chromosomal microduplication, raised the likelihood of an underlying ASD. The criteria for diagnosis of ASD according to the DSM-V describes “Persistent difficulties in the social use of verbal and nonverbal communication” as reflected in deficits involving domains such as social communication and knowing how to use verbal and nonverbal signals to regulate interaction (2). Additionally, the onset of symptoms needs to occur in the early developmental period (such as this patient with a reported early childhood speech delay). Indeed, once psychotic symptoms had subsided, the nature of encounters with the patient drastically changed to take on a presentation as described by these criteria. The patient displayed little ability to understand or engage in non-verbal communication, such as eye-contact, body language, or facing whom with which he was engaged in conversation. Other examples of the patient’s deficits in social interaction included failing to understand the inappropriate nature of asking each physician’s first name who entered the room and attempting to play a game he had created with evaluators, who were attempting to keep him focused on the medical interview. However, unlike during episodes, the patient was able to engage in conversation and follow a linear train of thought, without evidence of delusions, hallucinations, or disorganized speech. Notably, the DSM-V emphasizes that a diagnosis of schizophrenia can only be made in cases of concurrent autism spectrum disorder if there is specifically present prominent delusions or hallucinations during episodes. By viewing this patient’s presentation as episodes of psychosis (with accompanying hallucinations and delusions), due to schizophrenia, superimposed on autism spectrum disorder as gleaned from patient’s behavior between episodes, this patient’s combined presentation can be best understood.

The final suspected diagnosis on discharge was early-onset schizophrenia with underlying autism spectrum disorder. However, caretaker’s focus remained fixed on neurologic and/or autoimmune etiologies, despite discussions urging otherwise with mental health professionals. As a result, the choice was made not to pursue long-term medication treatment for the patient for psychiatric conditions, although he proved stable and without evidence of ongoing psychosis upon discharge. The recommendation to follow-up with more comprehensive psychiatric evaluation was again emphasized; however, it was unclear if this occurred due to the patient not returning to the current healthcare institution for further care.

Discussion
This report emphasizes how a variety of different components in a difficult medical case can create a lengthy and complicated road to diagnoses. In the case of children and adolescents when neuropsychiatric disorders are at question, a youngster’s continuing development complicates the course in ways that can affect behavior, emotions, cognition and general learning and development. Another component is how particular styles of parental interaction with their child and the healthcare system can pose challenges to concise diagnostic evaluation. Parent-child dynamics and socio-cultural milieu may also influence how children present symptoms; as it is, children’s presentations with psychiatric conditions are atypical and many children cannot describe or express their symptoms at all.

Many features of this patient’s medical history had raised suspicion for the possibility of factitious disorder imposed on another (2), namely the extensive, repeated prior medical workups with no significant findings; frequent consultation at a myriad of healthcare centers; failure for child to have clinical improvement despite considerable healthcare intervention and consultation; incongruences between reported patient history and indexed medical records; repeat history of refusing or withdrawing medication intervention despite physician recommendations. However, the patient’s real presence of medical illness, without the possibility of a fabricated condition, makes classic factitious disorder imposed on another more difficult to apply in this situation; however, considering psycho-dynamic aspects of that condition may help guide family interaction and care coordination.

Perhaps better applicable to this patient’s situation with respect to his parents is the concept of ‘emotional over-involvement’ on the part of the mother. In fact, the literature has shown that emotional over-involvement of caregivers that “manifests itself by over-emotionality, excessive self-sacrifice, over-identification, and extreme overprotective behavior with the patient” is correlated with higher risk of relapse and rehospitalization in those with schizophrenia (7). Therefore, by understanding this patient’s condition as schizophrenia, the relationship with his primary caregiver may contribute to explaining the excessive history of relapses and rehospitalization. Additionally, the failure to maintain a consistent anti-psychotic regimen could further account for this patient’s history of relapses. The mother, as primary caregiver, consistently stopped treatment that helped
the patient due to her belief that long-standing medication was ‘not what was best’ for her child and ‘unnecessary’ since he would ‘always get better on his own.’

The nature of the caretakers’ interactions further made psychiatric diagnoses difficult to explore in more depth, regarding a detailed family history, for example, even though psychiatric diagnosis was always considered a key of the differential diagnosis, the one of highest in clinical suspicion. Due to the inherent nature of psychiatric disorders, response to treatment yields key diagnostic information. A documented history of consistent parental discontinuation of psychiatric medications post-discharge, or even refusal during hospital-stay, presented barriers to fully exploring the psychiatric component of this patient’s presentation. In one particular example, during a presentation consistent with catatonia, providers gave a lorazepam challenge, with which the patient reportedly improved, further providing episodes of catatonia to evidence an overall diagnosis of schizophrenia. However, lorazepam had to be immediately discontinued due to parental refusal. Their perception was that the patient was not actually improving, when, by all other accounts, he objectively was. An additional element of caretaker interaction with the healthcare system to explore is the lack of pursuit of outpatient psychiatric evaluation, despite discharge recommendations following many inpatient admissions.

These observed behaviors from caretakers related to the patient’s care may have been the result of a variety of factors which complicate understanding of the relative contribution of each and how they interact with one another. In one element, physicians need to consider patient’s ability to simply access specialized healthcare services, such as may be required in the case of complex mental diagnoses. However, in this patient’s case, with residence in a highly populated, urbanized area, failure to have these services within a reasonable area of travel would be unlikely. However, this assumption does not incorporate access related to finances or transportation. In this sense, the extensive history of patient travel to prestigious medical centers and providers across a widely dispersed geographic region makes these forms of access limitation unlikely as well. The patient/caretaker’s sociocultural background also requires consideration in understanding their behaviors through navigating the healthcare system. Those within the Orthodox Jewish community have often reported fear of stigma originating within their community relating to mental health problems and the pursuit of care from mental health professionals (8). Studies have also demonstrated how members in these communities may feel dissuaded from recognizing or treating mental illness out of fear that this will negatively impact marriage prospects or go against religious tenets (9). Therefore, the failure to incorporate efforts to address these concerns into the care of this patient may have contributed to the course of care and caretaker behaviors, including the observed difficulty in shifting the focus of pursued healthcare services towards a psychiatric, rather than autoimmune or neurologic, focus.

Whenever the patient presented to a new provider for emergency work-up, initial clinical suspicions revolved around an autoimmune and metabolic encephalitis, even though numerous previous comprehensive work-ups either ruled-out these conditions or placed them at the lowest clinical suspicion. The fact that this diagnosis stayed with the patient may confirm the tendency of the parent to be repeatedly reporting these previous diagnoses as true. However, this finding may also demonstrate another element of the parental interaction that may have complicated the patient’s clinical picture: the use of an extensive list of different medical providers and specialists at a variety of different medical centers spread across the Northeastern United States. The patient’s having received medical care from such a variety of different medical providers, spread across time and space, introduces difficulties with communication between providers to get a better understanding of the patient’s prior medical care and clinical presentation. However, just as one may argue this difficulty as imposed by the caretaker’s decision to pursue healthcare in a variety of different places, so too may one view this difficulty as imposed by the failure of cohesive functioning across the healthcare system.

Complexities in caretaker interaction with the healthcare system need be investigated in relation to shortcomings of the healthcare system’s organization which can create barriers to efficient, comprehensive, continuous care. Inconsistencies in diagnoses and medical approaches, as evident across this patient’s medical record, can create mistrust in the healthcare system and physicians as a whole. Additionally, these inconsistencies can result in a lack of understanding of, and failure to appropriately value, conclusions drawn by healthcare providers at different moments in interaction with the healthcare system. A lack of clear communication of medical information across space and time, where elements of the patient’s history and prior medical information were lost, modified, or inappropriately added/maintained, through the medical record, can create confusion and frustration on the part of both the healthcare providers and parental caregivers, particularly when these coincide with a failure to observe significant improvement in the child. Indeed, medication non-adherence from parents with children requiring
psychiatric care has been found to correlate with an incongruency between parental expectations and physician’s recommendation as far as the duration and form of treatment (10). Furthermore, the effectiveness of the physician-parent relationship for the treatment of a child’s psychiatric illness can further be complicated in the way that changing parental needs and skills require the physician to similarly re-evaluate their approach (11). Without a cohesive medical history or a long-term physician-patient relationship, physicians may find difficulty in the ability to effectively communicate expectations and tailor their role within the framework of the parent’s skills/needs at that point in time.

Without ready access to previously documented medical information, future physicians may feel pressured to over-rely on patient’s ability to relay information about the medical history. A medical history as complex and long-standing as presented here complicates this process further, and can further pose as an obstacle to building an effective physician-patient relationship. Perhaps the ‘burden of proof’ to communicate not only the medical history, but also how or why these tests/diagnoses were attained, may be sensed by the patient/caregiver, which can impart a sense of disingenuity or incompetence in the healthcare provider or system as a whole. All of these elements together or individually may manifest in protracted duration of ineffectively or inefficiently treated disease, including recurrent psychosis and neurodevelopmental disorders. Additionally, these shortcomings may reflect in behavior by caregivers, such as emotional-overinvolvement, as a mechanism of protection or compensation for their loved ones, as a response to these shortcomings of the healthcare system.

Beyond the dynamics of parental interaction, this case emphasizes the importance of thoroughly reviewing prior medical records, especially in patients with longstanding, complicated histories of medical workup/intervention, since some test results may function better if re-interpreted given more contemporary knowledge and literature. In particular, this patient’s finding of a 15q11.5 microduplication in 2017 puts this idea into practice. At the time of the genetic test in 2017, interpretation of this finding was simply “Likely Benign,” with recommendation against further genetic testing for himself or relatives. Indeed, literature concerning this microduplication cites how “until recently these duplications were reported as variants of unknown significance,” even though more and more research has provided evidence to the contrary (14). Various studies have in fact demonstrated the correlation between this microduplication and speech delays, autism spectrum disorder (ASD), recurrent otitis media, sleep apnea, and OCD - features of each were found in this patient’s presentation (9-15). Despite actual documentation in the patient’s medical records of the correlation specifically between this microduplication and ASD during one encounter, subsequent records still defaulted back to the initial report interpretation of ‘likely benign.’ In fact, this chromosomal region has also been more generally identified as a ‘susceptibility locus’ for various neurodevelopment disorders beyond autism spectrum disorder including increased risk of schizophrenia (12, 13, 16, 17). Abnormalities at this chromosomal region have further been implicated in earlier age of onset for psychotic disorders including schizophrenia, which can help clinicians understand why this patient first presented at an unusually young age (18). Overall, the failure to fully reinterpret prior genetic test results served to potentially delay the eventual diagnosis of ASD as well as schizophrenia in this patient, since that information may have helped raise the clinical suspicion of these disorders to enable a more focused and efficient diagnostic investigation.

In other elements, this case also demonstrates the significant complexities of diagnosing co-morbid schizophrenia, with underlying ASD. In general, ASD must be often, if not always, considered in the cases of psychiatric workup for childhood psychosis, as it has been shown to create difficulties in diagnosing (19), or have a tendency to be mistaken for, psychotic illness (20). Moreover, the presence of baseline ASD may change the way that a co-morbid psychotic illness tends to present, as well as vice versa. Specifically, research has found evidence supporting that “individuals with ASD who have also developed a comorbid psychotic illness differ significantly in their autistic phenotypic profile from individuals with ASD alone, particularly through significantly fewer lifetime stereotyped, repetitive or restrictive interests/behaviors, as is displayed with this patient’s presentation (21). Moreover, ASD individuals tended to have more acute, transient psychosis courses compared to the non-ASD population (22).

As a whole, patients with a prior history of a longstanding, complex, and fluctuating clinical picture present unique challenges in diagnostic investigation. The case of this patient specifically illustrates the importance of an understanding of how co-morbid illnesses, muddled histories, and poor reporting and communication, increase the complexity of the case, particularly if psychiatric symptoms are involved. Great stigma surrounds psychiatric illness. Clinician must always re-evaluate prior finding in light of new scientific information, and tactfully know how to navigate complex parental dynamics in the cases of children and adolescents. Further the case illustrates how lack of
communication among providers, lack of a really unified medical record and not letting the evidence speak for itself in terms of where it leads diagnostically can not only harm the patient but also present unnecessary and wasteful costs to the medical system due to duplication of effort to no further avail.

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Declaration of interest
The authors report no conflicts of interest.

Statement of consent
Parental consent on behalf of the patient was obtained with regards to the execution and subsequent publication of this case report. Every attempt has been made to ensure anonymity including removal of patient identifiers that include names, dates, and locations of care.

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