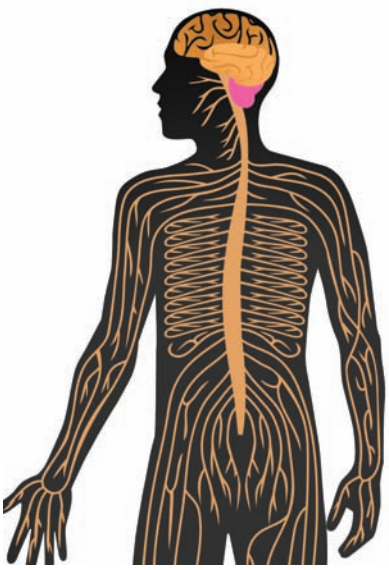

REVIEW

Neurosarcoidosis and the Complexity in its Differential Diagnoses: A Review

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ABSTRACT

While uncommon, neurosarcoidosis has been reported to present similarly to schizophrenia, with auditory hallucinations and delusions. We review the evaluation and work-up of neurosarcoidosis and discuss the differential diagnoses of these psychotic symptoms.

AN OVERVIEW OF NEUROSARCOIDOSIS

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology. The illness preferentially affects African Americans, with reports of a 3- to 4-fold increase compared to Caucasians.[1] Neurosarcoidosis (NS) is the neurologic manifestation of sarcoidosis, a granulomatous inflammatory disease, which although most often affects the lungs, can also affect the eyes, skin, liver, spleen, and nervous system.[2] Table 1 lists diagnostic criteria for NS. Neurosarcoidosis affects 5 to 15 percent of sarcoidosis patients.[3] Depending on the anatomic location, NS symptoms can range from peripheral neuropathy to more central features, including memory loss and changes in mood and/or behavior. Psychiatric manifestations, include, but are not limited to, delirium and psychosis,[4,5] and have been reported to occur in 20 percent of patients with NS or one percent of all those affected with sarcoidosis.[6] Sarcoidosis is comparable to the lifetime prevalence of schizophrenia, which ranges from 0.59 to 1.46 percent of the general population.[7] Furthermore, one study reported that 2 of 268 patients with first-episode schizophrenia had NS.[8]

Behavioral changes are one of the least common manifestations of neurosarcoidosis, occurring in only 20 percent of patients with neurosarcoidosis, or one percent of all those affected with sarcoidosis.[6] However, when it does occur, it can cause a very vivid psychosis, such as auditory and visual hallucinations (A/VH) and delusions.[8] Granulomatous infiltration of the central nervous system (CNS) may produce a wide variety of neuropsychiatric symptoms, including A/VH. Additionally, diffuse cerebral vasculopathy may produce psychosis or dementia. Thus, in a patient with multisystem sarcoidosis and unexplained mental deterioration, evaluation of the CNS is indicated.[9]

There is no pathognomonic feature to diagnose neurosarcoidosis, save brain biopsy

revealing noncaseating granulomas. Table 2 summarizes the neurological evaluation of NS. Diagnosing neurosarcoidosis initially relies heavily on maintaining a high index of clinical suspicion for all patients with sarcoidosis and comorbid neurologic and/or psychiatric symptoms. In NS, magnetic resonance imaging (MRI) of the head may demonstrate leptomeningeal involvement or other intracranial findings including, punctuate foci in white matter. The former has only been reported, however, in 38 to 40 percent of patients with NS.[10,11] Unfortunately, white matter lesions are nonspecific and resemble lesions seen with multiple sclerosis, vasculitides, microvascular disease, and infectious etiologies, such as Lyme disease. It is unclear whether these reflect periventricular granulomas or small areas of infarction related to granulomatous vasculopathy. These lesions typically do not correlate well with clinical symptoms, and do not reverse with treatment or symptomatic improvement.[12] In fact, in one study, 100 percent of white matter lesions did not correlate to any symptoms of NS.[13] Thus, despite an overall high sensitivity (82–97%) of white matter disease and other brain MRI findings,[14] brain MRI lacks specificity in diagnosing NS.[15]

Cerebrospinal fluid (CSF) abnormalities in NS are usually nonspecific and include mild pleocytosis, high protein count, elevated angiotensin converting enzyme (ACE) levels (serum ACE levels can also be elevated) and sometimes, slightly low glucose. First, studies report that 20 to 33 percent of NS patients have normal CSF.[16,17] Additionally, sensitivity of serum ACE in NS varies from 24 to 76 percent.[16] Furthermore, the specificity and sensitivity of CSF ACE for NS is controversial. One study found that 55 percent of patients with neurosarcoidosis, five percent of systemic sarcoidosis patients, and 13 percent of patients with other diseases showed increases in CSF-ACE levels. Overall, CSF-ACE levels are insensitive (24–55%) for the diagnosis of NS though they may be relatively specific (94–95%).[12] Finally, there seems to be little relation found between serum and CSF concentrations of ACE in patients with neurosarcoidosis, nor is there any relation between serum concentrations and the clinical picture and CSF-total protein or CSF-albumin (increase of albumin concentration in the CSF is an indicator of functioning of the blood brain barrier). Thus, ACE in the CSF is most probably synthesized in the nervous system and released by sarcoid granulomas in the CNS[16] and not by passive transfer from the serum.[12] But, CSF-ACE levels seem to be useful in the monitoring of disease activity and treatment response.[16]

Seizures have been reported to occur in about 20 percent of NS patients and an initial neurological feature in 10 percent. Seizures in sarcoidosis are often thought to reflect serious brain pathology (e.g., mass lesions, hydrocephalus, encephalopathy, or vasculopathy). Electroencephalogram (EEG) may demonstrate paroxysmal activity or generalized slowing/ disorganization.[18] The latter could support a diagnosis of meningoencephalitis, while the former could support seizures. One limitation in a nonsleep-deprived EEG is that the latter can induce a clinical state that is considered a precipitant of epileptic seizures; interictal seizures have been detected in 13 to 52 percent of patients with normal or inconclusive initial routine EEG.[19]

Hypercalcemia has been reported in 13 percent of patients with multisystem sarcoidosis,[16] although depending on the population studied, this may range from 2 to 63 percent.[20] Furthermore, hypercalcemia can cause psychotic symptoms. The severity of these symptoms increases directly proportional to serum calcium levels; however, symptoms typically occur between 12 to 16mg/dL.[21] Hypercalcemia could be due to the uncontrolled synthesis of 1,25-dihydroxyvitamin D3 by macrophages as 1,25-dihydroxyvitamin D3 leads to an increased absorption of calcium in the intestine and to an increased resorption of calcium in the bone. Immunoregulatory properties have been ascribed to 1,25-dihydroxyvitamin D3. It is an important inhibitor of interleukin-2 and of interferon-gamma-synthesis, two cytokines that are important in granuloma formation in sarcoidosis.[20]

CASE VIGNETTE

We were asked to consult on a 31-year-old African-American woman with index admission, biopsy-proven systemic sarcoidosis. In addition to new-onset sarcoidosis, she had a two-month history of acute onset A/VH and paranoid delusions. The patient denied alcohol or illicit drug usage. Both urine drug screen and blood alcohol on admission were negative. Her family history was significant for schizophrenia. She scored a 6 on the severity sub-section of the Neuropsychiatric Inventory Questionnaire (NPI-Q/S),[22] scoring only on questions concerning delusions and hallucinations. She scored 26/30 on the Mini Mental State Examination.[23] Table 2 lists pertinent positives and negatives in this patient's evaluation of NS.

The patient was started on prednisone 60mg daily, which was decreased to 40mg daily after three days, to minimize psychiatric complications, including psychosis. We began her on olanzapine 5mg twice daily for A/VH and delusions. This corresponded to Day 5 of treatment with prednisone 40mg/day. Her NPI-Q/S score was 3 by Day 4 of treatment with olanzapine (and a total of 12 days of prednisone therapy), and by hospital discharge, her NPI-Q/S score was 0 one week after initiating olanzapine treatment.

TABLE 1. Classification of definite, probable, and possible NS[15]

NS can be diagnosed in patients with (i) a clinical presentation suggestive of NS with (ii) exclusion of other possible diagnoses, as follows:

1. Definite NS: Positive central nervous system histology

2. Probable NS: [a] Laboratory evidence of CNS inflammation (elevated levels of CSF protein and/or cells, the presence of oligoclonal bands and/or MRI evidence compatible with neurosarcoidosis), and [b] Evidence for systemic sarcoidosis (either through positive histology, including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging and serum ACE)

3. Possible NS: Where the above criteria are not met

Abbreviations—NS: neurosarcoidosis; CNS: central nervous system; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; ACE: angiotensin converting enzyme

DIAGNOSIS, DIFFERENTIAL DIAGNOSES, AND TREATMENT

Histopathologic examination of involved CNS tissue remains the gold standard for diagnosing neurosarcoidosis. From a therapeutic standpoint, neurosurgery is indicated only when medications fail or when life-threatening emergencies arise. In suspected cases of NS, with extraneural tissue biopsy-confirmed systemic sarcoidosis, early treatment is advocated due to the mortality rate of 1 to 5 percent. Additionally, potential fibrotic and microischemic changes may result in permanent CNS damage.[12]

While beyond the scope of this article, corticosteroid (CS) therapy remains first-line treatment for NS with second-line therapy being other immunosuppressive agents, such as azathioprine and methotrexate.[3] Given there is only one-percent incidence of psychosis in sarcoidoisis, and this rate does not differ significantly from the base rate of schizophrenia in the general population, it is conceivable that psychosis and sarcoidoisis are unrelated, although it is difficult to obtain accurate population statistics when base rates are so low and many cases may be missed. Regardless, some,[24–27] but not all,[11] studies support corticosteroid-responsive behavioral disturbances and psychosis in patients with NS. However, except case reports that report successful treatment of psychosis in NS with both conventional and atypical antipsychotics,[28,29] there is a dearth of current evidence in the literature to guide physicians in the treatment of this clinical state. The vignette patient began olanzapine adjunctively to CS after eight days of CS treatment. Thus, given the reported efficacy of both medications treating psychotic disorder due to NS, we can only state her psychotic symptoms abated; whether this was due to either or both olanzapine and prednisone concomitantly is unknown. Careful attention should be given to those patients with NS being treated with corticosteroids due to the known dose-related risk of developing psychiatric symptoms with CS,[30] which can mimic the psychotic symptoms of NS.

Alternatively, inflammatory processes have been posited in the pathogenesis of both sarcoidosis and schizophrenia. An interesting (inflammatory-based) parallel between both conditions is that there is a blunted response of the skin to different antigens. In schizophrenia, this has been observed before the era of antipsychotics. This finding has been replicated in unmedicated patients with schizophrenia using a skin test of the cellular immune response, intimating a markedly attenuated *in-vivo,* type-1-mediated, cellular immune response in patients with schizophrenia, supporting a hypothesis of a relative T-helper 2 (Th2) shift in schizophrenia.[31] In sarcoidosis, however, this "immune paradox" occurs despite an intense immune T-helper 1 (Th1) response in the organ involved.[32]

In sarcoidosis, the immune process seems to begin with an antigenic stimulus, followed by T-cell and macrophage activation via a classic major histocompatibility complex (MHC) II–mediated pathway. This process has all of the features of a classic Th1 response (i.e., type-1 immune response), and in fact, sarcoidosis may be the first disorder to be clearly identified as a Th1-mediated disease. As part of this process, pro-inflammatory cytokines are released (including, Interferon-γ (IFNγ), Tumor necrosis factor-α (TNFα), Interleukin (IL)-1β IL-2, IL-6)[33] that recruit cells to sites of granuloma formation and trigger activation of these cells. In some instances, there may be a disruption of the normal function of regulatory cells and/or persistence of the antigen that allows the granulomas progress instead of resolving, as they do in most patients. The local environment of the granulomas may eventually change to a more Th2 (type-2 immune response)-like environment, with the release of anti-inflammatory cytokines, such as IL-4 and IL-10, that decreases the intensity of granuloma formation but favors the development of fibrosis.[32]

The possible influence of an immunological process for the pathogenesis of schizophrenia resulting in inflammation is in its infancy. A well-established finding in schizophrenia is the decreased *in-vitro* production of IFN-γ, reflecting a blunted production of type-1 cytokines. Nonetheless, several reports have described increased serum IL-6 levels in schizophrenia. IL-6 serum levels might be especially high in patients with an unfavorable course of the disease and in patients

with a long duration of the disease. It can be hypothesized that the blunted type-1 response is found primarily in early stages of schizophrenia, while a chronic pro-inflammatory stage with an accentuation of the type-2 response including high IL-6 levels may predominate in later stages.[34]

Schizophrenia is a disorder of dopaminergic neurotransmission, but modulation of the dopaminergic system by glutamatergic neurotransmission seems to play a key role. Glutamatergic hypofunction, however, is mediated by the N-methyl-D-aspartate (NMDA)-receptor antagonism. The only endogenous NMDA receptor antagonist identified up to now is kynurenic acid (KYNA). KYNA levels are described to be higher in the CSF and in critical CNS regions in patients with schizophrenia as compared to controls. As a result of its NMDA receptor antagonism, increased KYNA levels have been reported to explain psychotic symptoms and cognitive deterioration.[35]

Additionally, another line of evidence suggests that a (prenatal) infection is involved in the pathogenesis of schizophrenia. Due to an early sensitization process of the immune system or to a (chronic) infection, which is not cleared through the immune response, an immune imbalance between the type-1 and the type-2 immune responses takes place in schizophrenia. The type-1 response is partially inhibited, while the type-2 response is over-activated. This immune constellation is associated with inhibition of the enzyme indoleamine dioxygenase (IDO), because IDO—located in astrocytes and microglial cells—is inhibited by type-2 cytokines. IDO catalyzes the first step in tryptophan metabolism, the degradation from tryptophan to kynurenine. Downstream, this results in an accumulation of KYNA in critical CNS regions. Thus, the immune-mediated glutamatergic-dopaminergic dysregulation may lead to the clinical symptoms of schizophrenia.[35]

Thus, in sarcoidosis and schizophrenia, increase in type-2 response is over-activated, especially in the later stages of both illnesses. And while the type-2 response is typically anti-inflammatory, IL-6, a pro-inflammatory cytokine, is a product of activated monocytes and has been referred to as a marker of the type-2 immune response.[34] Thus, through increased activity of IL-6 (and potentially other proinflammatory cytokines), white and grey matter degeneration in schizophrenia, and granuloma formation with possible development of fibrosis in the CNS of sarcoidosis patients, may provide putative evidence of a causal link between sarcoidosis and psychosis.

Psychiatrically, schizophreniform disorder and, depending on

TABLE 2. Neurological work-up for NS and pertinent positives and negatives in vignette patient[4,17,42–44]

TESTS/IMAGING	FINDINGS IN NEUROSARCOIDOSIS	PATIENT FINDINGS
Gadolinium-contrast MRI of the brain	T1 weighted: • Leptomeningeal enhancement -especially basilar meninges • Hypothalamic enhancement • Pituitary gland enhancement • Cranial Nerve enhancement -especially CN II • Hydrocephalus T2 weighted: • Nonenhancing periventricular white matter lesions • Enhancing parenchymal lesions	T1 weighted: • No evidence of abnormal leptomeningeal or parenchymal enhancement
Gadolinium-contrast MRI of the spine	T1 weighted: • Fusiform enlargement of spinal cord • Low signal intensity • Leptomeningeal enhancement T2 weighted: • Fusiform enlargement of spinal cord • High signal intensity	Noncontrast (cervical): • No evidence of leptomeningeal disease T1 weighted (thoracic): • Several enhancing foci in the midthoracic spine, not definitive for neurosarcoidosis T1/T2 weighted (lumbar): • Slightly prominent, nondiagnostic, signal in cauda equina without nodularity
Lumbar puncture	• Increased protein • Decreased glucose • Increased lymphocytes -CD4: CD8 ratio >5 • Elevated ACE level (nonspecific) • Oligoclonal bands (rare)	• Protein: 14.9mg/dL • Glucose: 114mg/dL • WBC count: 0
EEG	• Acute encephalomeningitis - early stages • Epileptic discharges	No abnormalities
EMG and nerve conduction studies	• Myopathy • Peripheral neuropathy -symmetric axonal polyneuropathy -chronic sensorimotor neuropathy -atypical neuropathies mononeuritis multiplex	EMG: • Bilateral denervation of the extensor hallicus longus consistent with mononeuritis multiplex
18FDG PET of brain	• Areas of hyper/hypometabolism -helpful for selecting biopsy location	Not performed

Abbreviations—NS: neurosarcoidosis; MRI: magnetic resonance imaging; ACE: angiotensin-converting enzyme; WBC: white blood cell; EEG: electroencephalogram; EMG: electromyography; 18FDG PET: 18F-fluorodeoxyglucose positron-emission tomography

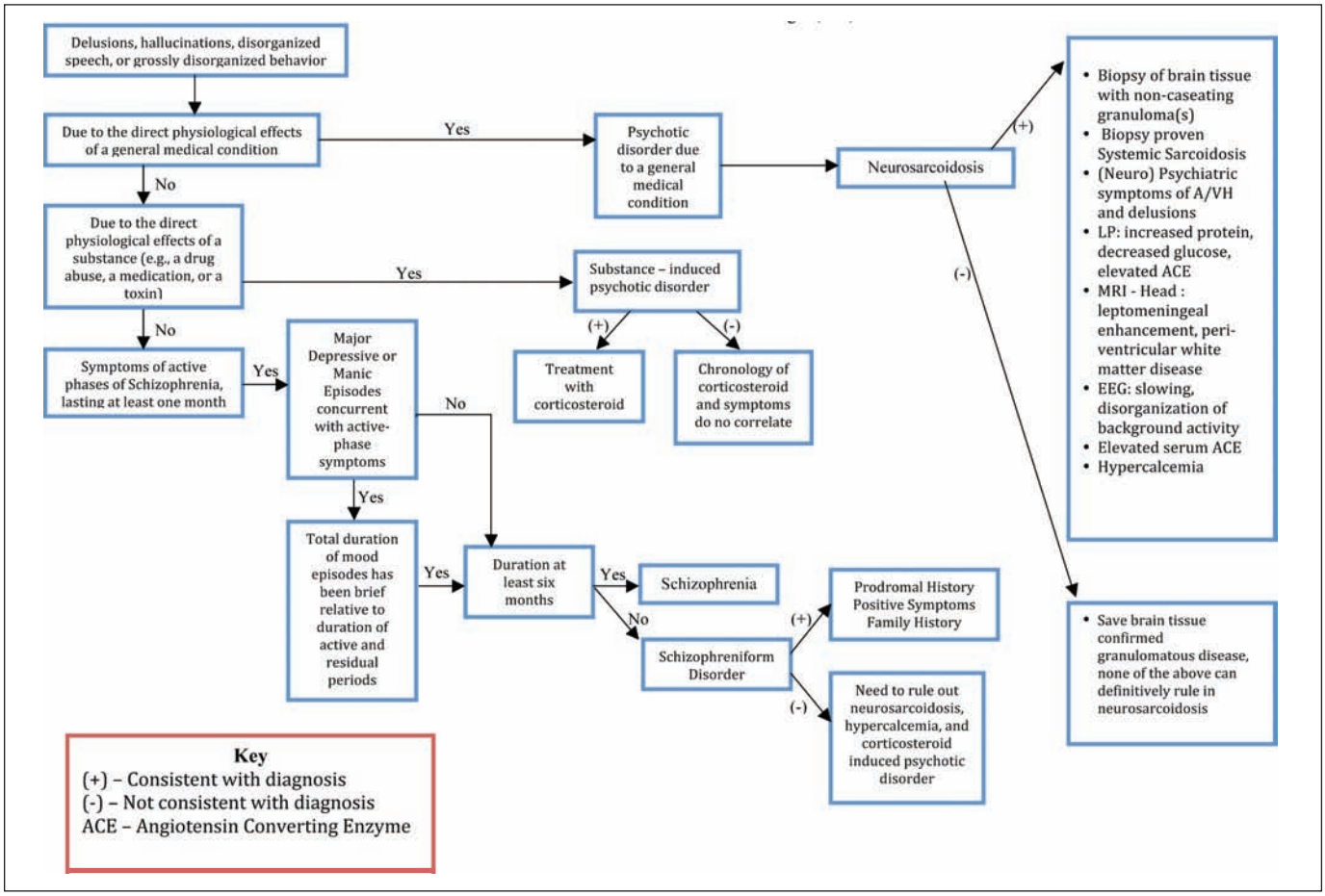

FIGURE 1. Differential diagnosis of psychotic disorders in neurosarcoidosis. Derived from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC, American Psychiatric Press, Inc.; 2000.

longitudinal course, schizophrenia need be considered in the differential diagnoses of psychotic phenomenology in NS. For instance, in a sample of 268 cases of first-episode schizophrenia, 15 patients were found to have an underlying medical condition that appeared relevant to the mental state (furthermore, and relevant to this case vignette, 2 of those 15 patients were diagnosed with neurosarcoidosis).[36] Although, in a sample of over 630,000 encounters of patients with psychosis, 2 out of 3 of these patients were diagnosed with schizophrenia, one-quarter with bipolar disorder, with only 2.5 percent diagnosed with psychosis due to a general medical condition;[37] however, other studies report this number to be as high as 20 percent.[6]

Clinically, the psychotic symptoms of the patient in the vignette were attenuated, seemingly to CS and olanzapine; however, given the relatively concurrent administration of both medications, the actual agent(s) responsible for treatment success will never be truly known. Thus, treatment response is not particularly useful in delineating our patient's ultimate diagnoses, especially given that psychotic disorder due to NS has been reported to respond to both CS and antipsychotics, individually and adjunctively.[24–29] Additionally, substantial proportions of first-episode patients with schizophrenia have showed clinically meaningful response and remission rates within 12 months with antipsychotics.[38] Finally, our patient also presented with positive symptoms, which have been reported to respond very well to antipsychotic treatment, whereas other dimensions of schizophrenia psychopathology tend to be less responsive, i.e., negative and cognitive symptoms, as well as disorganization.[39]

CONCLUSION

In closing, this review delineates the difficult and complex differential diagnoses of psychoses in NS. Figure 1 illustrates the differential diagnoses for psychotic disorders. These diagnoses include psychotic disorder due to neurosarcoidosis (as well as resultant, hypercalcemia), corticosteroid-induced psychotic disorder, and depending on duration of symptoms, schizophreniform disorder or schizophrenia. Additionally, any/all of the aforementioned conditions can contribute to this complex underlying clinical picture.

Before ascribing any of the above diagnoses, a caveat is that NS is more common in Africans and people of African descent than in people of any other race. In the

United States, the ratio of affected African Americans to affected Caucasians ranges from 10:1 to 17:1.[40] Additionally, race and ethnicity seem to have an effect on the diagnosis of psychotic disorders. For instance, in one study, about three-quarters of African American psychiatric patients received a psychosis diagnosis as compared to about one-half of Caucasian native-born, Caucasian migrant, or other minority migrant patients. Controlling for gender and age, African American psychiatric inpatients were approximately 3 to 4 times more likely to receive a psychosis diagnosis as compared with patients in the other three groups.[41]

In sum, both sarcoidosis and NS preferentially affects African Americans. As NS can present with psychotic phenomenology and given the tendency of African-Americans to be diagnosed with psychotic disorders, the discussed differential diagnosis need be fully considered, before hastily applying any diagnosis to an affected patient.

The patient vignette also illustrates that, as per the diathesis-stress model, the "stress" of NS (with or without hypercalcemia and CS administration) to a patient's "diathesis" (family history) toward psychosis, could precipitate emergence of psychotic symptoms. As to whether these psychotic symptoms are related or unrelated to underlying neurosarcoidosis, remains an unresolved issue.

REFERENCES

1. Ligon CB, Judson MA. Impact of systemic corticosteroids on healthcare utilization in patients with sarcoidosis. *Am J Med Sci.* 2011;341(3):196–201.
2. Ahn SW, Kim KT, Youn YC, et al. Isolated spinal cord neurosarcoidosis diagnosed by cord biopsy and thalidomide trial. *J Korean Med Sci.* 2011;26(1):154–157.
3. Hamzeh N. Sarcoidosis. *Med Clin North Am.* 2011;95(6):1223–1234.
4. Joseph FG, Scolding NJ. Sarcoidosis of the nervous system. *Pract Neurol.* 2007;7(4):234–244.
5. Spiegel DR, Thomas CS, Shah P, et al. A possible case of mixed mania due to neurosarcoidosis treated successfully with methylprednisolone and ziprasidone: another example of frontal-subcortical disinhibition? *Gen Hosp Psychiatry.* 2010;32(3):342.e1–3.
6. Duwe BV, Turetsky BI. Misdiagnosis of schizophrenia in a patient with psychotic symptoms. *Neuropsychiatry Neuropsychol Behav Neurol.* 2002;15(4):252–260.
7. Vanasse A, Courteau J, Fleury MJ, et al. Treatment prevalence and incidence of schizophrenia in quebec using a population health services perspective: different algorithms, different estimates. *Soc Psychiatry Epidemiol.* 2011 Mar 29. [Epub ahead of print]
8. Westhout FD, Linskey ME. Obstructive hydrocephalus and progressive psychosis: rare presentations of neurosarcoidosis. *Surgical Neurology.* 2008:69(3):288–292.
9. Hoitsma E, Drent M, Sharma OP. A pragmatic approach to diagnosing and treating neurosarcoidosis in the 21st century. *Curr Opin Pulm Med.* 2010;16(5):472–479.
10. Ginat DT, Dhillon G, Almast J. Magnetic resonance imaging of neurosarcoidosis. *J Clin Imaging Sci.* 2011;1:15. Epub 2011 Feb 11
11. Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis—diagnosis and management. *QJM.* 1999;92(2):103–117.
12. Terushkin V, Stern BJ, Judson MA, et al. Neurosarcoidosis: presentations and management. *Neurologist.* 2010;16(1):2–15.
13. Shah R, Roberson GH, Curé JK. Correlation of MR imaging findings and clinical manifestations in neurosarcoidosis. *AJNR Am J Neuroradiol.* 2009;30(5):953–961.
14. Gullapalli D, Phillips LH. Neurologic manifestations of sarcoidosis. *Neurology Clinics.* 2002;20(1):59–83.
15. Pawate S, Moses H, Sriram S. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. *QJM.* 2009;102(7):449–460.
16. Hoitsma E, Faber CG, Drent M et al. Neurosarcoidosis: a clinical dilemma. *Lancet Neurol.* 2004;3(7):397–407.
17. Gullapalli D, Phillips LH 2nd. Neurosarcoidosis. *Curr Neurol Neurosci Rep.* 2004;4(6):441–447.
18. Joseph FG, Scolding NJ. Neurosarcoidosis: a study of 30 new cases. *J Neurol Neurosurg Psychiatry.* 2009;80(3):297–304.
19. Gandelman-Marton R, Theitler J. When should a sleep-deprived EEG be performed following a presumed first seizure in adults? *Acta Neurol Scand.* 2011;124(3):202–205.
20. Ackermann D. Hypercalcemia in sarcoidosis—case report, prevalence, pathophysiology and therapeutic options. *Ther Umsch.* 2007;64(5):281–286.
21. Chiba Y, Satoh K, Ueda S, et al. Marked improvement of psychiatric symptoms after parathyroidectomy in elderly primary hyperparathyroidism. *Endocr J.* 2007;54(3):379–383.
22. Kaufer DI, Cummings JL, Ketchel P,et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci.* 2000;12:233–239.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state:" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189–198.
24. Allen RK, Sellars RE, Sandstrom PA. A prospective study of 32 patients with neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2003;20(2):118–125.
25. De Mulder D, Vandenberghe J. Neurosarcoidosis as a cause of manic psychosis. *Tijdschr Psychiatr.* 2008;50(11):741–745.
26. O'Brien GM, Baughman RP, Broderick JP, et al. Paranoid

psychosis due to neurosarcoidosis. Sarcoidosis. 1994;11(1):34–36.
27. Bona JR, Fackler SM, Fendley MJ, et al. Neurosarcoidosis as a cause of refractory psychosis: a complicated case report. *Am J Psychiatry.* 1998;155(8):1106–1108.
28. Bourgeois JA, Maddock RJ, Rogers L, et al. Neurosarcoidosis and delirium. *Psychosomatics.* 2005;46(2):148–150.
29. Popli AP. Risperidone for the treatment of psychosis associated with neurosarcoidosis. *J Clin Psychopharmacol.* 1997;17(2):132–133.
30. Acute adverse reactions to prednisone in relation to dosage. *Clin Pharmacol Ther.* 1972;13(5):694–698. [No authors listed]
31. Riedel M, Spellmann I, Schwarz MJ et al. Decreased T cellular immune response in schizophrenic patients. *J Psychiatr Res.* 2007;41(1–2):3–7.
32. Gerke AK, Hunninghake G. The immunology of sarcoidosis. *Clin Chest Med.* 2008:29(3):379–390.
33. Janssen DG, Caniato RN, Verster JC, et al. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Hum Psychopharmacol.* 2010;25(3):201–215.
34. Müller N, Schwarz M. Immune System and schizophrenia. *Curr Immunol Rev.* 2010;6(3):213–220.
35. Muller N, Schwarz M. Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. *Neurotox Res.* 2006;10(2):131–148.
36. Johnstone EC, Macmillan JF, Crow TJ. The occurrence of organic disease of possible or probable etiological significance in a population of 268 cases of first episode schizophrenia. *Psychol Med.* 1987;17(2):371–379.
37. Charles J, Miller G, Ng A. Management of psychosis in Australian general practice. *Aust Fam Physician.* 2006;35(3):88–89.
38. Boter H, Peuskens J, Libiger J, et al. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). *Schizophr Res.* 2009;115(2–3):97–103.
39. Schennach-Wolff R, Jäger M, Mayr A, et al. Predictors of response and remission in the acute treatment of first-episode schizophrenia patients—Is it all about early response? *European Neuropsychopharmacology.* 2011;21(5):370–378.
40. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med.* 2001;164(10 Pt 1):1885.
41. Jarvis GE, Toniolo I, Ryder AG, et al. High rates of psychosis for black inpatients in Padua and Montreal: different contexts, similar findings. *Soc Psychiatry Psychiatr Epidemiol.* 2011;46(3):247–253.
42. Smith JK, Matheus MG, Castillo M. Imaging manifestations of neurosarcoidosis. *AJR Am J Roentgenol.* 2004;182(2):289–295.
43. Zuniga G, Ropper AH, Frank J. Sarcoid peripheral neuropathy. *Neurology.* 1991;41(10):1558–1561.
44. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med.* 2007;357(21):2153–2165. ■