Does a Kind of Over-Fitting Occur in the Brain of Autistic Patients?

To the Editor: Autism is a biological disorder with a clinical onset in the first years of life that persists, to varying degrees, throughout the lifetime. It is characterized by abnormality in reciprocal social interaction, communication, and language development as well as by repetitive and stereotyped behavior. These abnormalities are caused by defects in multiple areas of the brain. Although intense effort has been invested in discovering a physical cause for the etiology of autism, no one has yet succeeded. We are still a long way from claiming the knowledge of causality.[1]

Reduced generalization has been noted in autism for many decades.[2] This key feature of people with autism can also be viewed from the perspective of artificial neural networks.

Artificial neural networks have been around since the seminal papers of McCulloch and Pitts[3] and Rosenblatt.[4] Many neural network models have been proposed and investigated. Artificial neural networks are built by using simplified models of biological neurons. The pattern of connections between the neural units is most often established via learning rules and gives the network its ability to compute complex functions and to develop emergent behaviors.

One problem that occurs during neural network training is overfitting—the error on the training set is driven to a very small value, but when new data are presented to the network, the error is large. In other words, the network has memorized the training examples, but it has not learned to generalize and find the true answer in new situations.

This overfitting in artificial neural networks is, to some extent, similar to what happens in the biological neural networks of the brain in people with autism. In other words, the interest that autistic persons show toward lawful and highly predictable systems[5] produces a situation that is analogous to overfitting. When overfitting happens in artificial neural networks, the network learns precisely the relationship between inputs and outputs in the training set, but it does not have the ability to adapt to novel circumstances. Consequently the generalization ability of the network is poor.

A memorizing procedure rather than learning happens in the brain of an autistic patient. Therefore, such a patient is not capable of incorporating prior knowledge in the learning process. This is in accordance with change resistance, need for sameness, and low generalization features of autistic persons.

Taking this similarity between artificial neural networks and autism into consideration may lead to novel learning procedures for these patients. For example, increasing the training set (i.e., the different situations to which the patient is exposed) and/or early stopping (i.e., reducing the intense concentration on training experiences) may be proper strategies in managing autistic patients.

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Cerebral Venous Sinus Thrombosis May Be Associated With Clozapine

To the Editor: Recent reports suggest that atypical antipsychotics are associated with increased risk of cerebrovascular adverse events, such as stroke, particularly in older people with dementia,[1] though the mechanisms remain unknown. We describe a case of cerebral venous sinus thrombosis likely to be associated with clozapine, which to our knowledge has not been previously reported.

Case Report

A 39-year-old woman with chronic schizophrenia was admitted with a relapse of psychotic symptoms having previously been stable on depot flupentixol for many years. Her psychosis was resistant to increased doses of oral flupentixol and risperidone. Her medications were changed to clozapine, and during the second week of dose escalation (at 100 mg b.i.d.), she developed an acute right hemiparesis and visual field loss. A CT scan several days later showed left parieto-occipital infarction, but the images were degraded by motion. A provi-

sional diagnosis of ischemic stroke was made. Routine biochemical, renal, liver, bone, lipid, hematology, and thyroid profiles; erythrocyte sedimentation rate; C-reactive protein; ECG; chest X-ray; transthoracic echocardiography; and extracranial Doppler studies were normal. Her only vascular risk factors were smoking 20 cigarettes per day and a history of stroke in her father.

An MRI 10 days later showed evidence of thrombus within the sagittal sinus, with left parieto-occipital infarction (Figure 1, panels A and B). Clozapine treatment was ceased, and the hemiparesis resolved over 1 month. A repeat MRI 2 months after symptom onset demonstrated recanalization of the sagittal sinus and near-resolution of the parieto-occipital abnormality (Figure 1, panels C and D), supporting the diagnosis of cerebral venous sinus thrombosis and venous infarction.

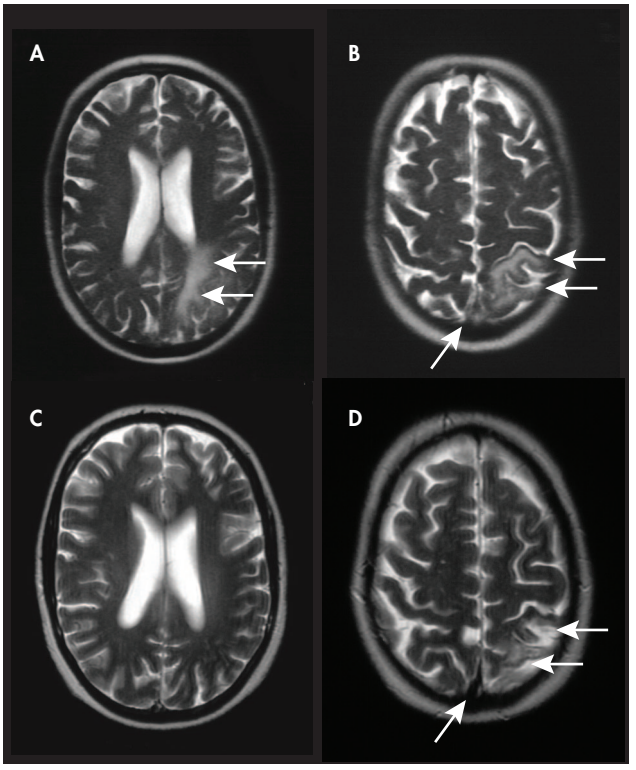
Discussion

No prothrombotic risk factors could be identified: she had not been dehydrated, detailed thrombophilia screening (including protein C, S, antithrombin III, Factor V Leiden, anticardiolipin antibodies) was negative, there was no systemic malignancy, and she was not taking the contraceptive pill. We therefore suggest that the cerebral venous sinus thrombosis may have been related to the recent introduction of clozapine.

Antipsychotic medications are associated with pulmonary and deep vein thrombosis, and clozapine in particular has been associated with fatal thromboembolism.[2] Recent case-control studies have shown an increased risk of venous thromboembolism in antipsychotic-treated patients under 60 years old, especially with atypical agents.[3] Postulated mechanisms include drug-induced sedation, obesity, antiphospholipid antibodies, and activation of the coagulation system.[4] To date, there have been no previous reports of cerebral venous thrombosis associated with antipsychotic medication.

Cerebral venous thrombosis and venous infarction can easily be missed or mistaken for arterial ischemic stroke. The clinical presentation is extremely variable, though headache, seizures, papilledema, and focal neurological symptoms are common. Recognition is vital since anticoagulation may be indicated for ischemic stroke. Our report suggests a possible association between cerebral venous thrombosis and antipsychotic medication. Thus, we recommend that a diagnosis of cerebral venous thrombosis should be considered in patients on antipsychotic medications who present with stroke-like symptoms without significant vascular risk factors.

FIGURE 1. Axial T2-Weighted MRI of a Patient



The left of the brain is on the right side of each panel. Panels A and B are images from T2-weighted sequences two weeks after onset of an acute right hemiparesis. Note the high signal in the sagittal sinus (arrow, B) and in the left parieto-occipital region (arrows, A and B), which does not conform to a single arterial territory, does not extend out to the cerebral cortex, and is consistent with venous infarction. Panels C and D are from T2-weighted sequences acquired two months later; by contrast, these images show a normal flow void (dark) in the sagittal sinus (arrow, D), with little abnormal signal in the left parieto-occipital region.

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Clozapine-Induced Negative Myoclonus is not Cataplexy

To the Editor: Desarkar et al.[1] describe a patient who developed negative motor symptoms (sudden knee-buckling and dropping of objects) while taking clozapine. Similar cases have been reported by others,[2] and I have seen several cases as well. This phenomenon has been termed incorrectly cataplexy. True cataplexy is "specific to narcolepsy and . . . characterized by a sudden drop of muscle tone triggered by emotional factors."[3] Because clozapine-related intermittent loss of muscle tone is not preceded by strong emotion, and occurs in patients demonstrating no other evidence of narcolepsy (nor any evidence of a brainstem or hypothalamic lesion known to produce rare cases of secondary cataplexy[3]), it is inaccurate on purely semantic grounds to call this phenomenon cataplexy. A more accurate term is negative myoclonus, which has been defined as "a motor phenomenon characterized by involuntary jerky movement due to brief, sudden interruption of muscle activity."[4] Negative myoclonus can be seen in clinical conditions ranging from epilepsy to toxic-metabolic encephalopathies such as hepatic encephalopathy (in which case it is known as asterixis).[4]

Accurate terminology points the way toward better understanding the pathophysiology of clozapine-induced negative myoclonus. It is important to consider the possibility that clozapine-induced negative myoclonus, like clozapine-induced positive myoclonus, could be an epileptic phenomenon predictive of the development of other seizure types including generalized tonic-clonic convulsions.[5] In Desarkar et al.'s[1] study, the patient's nonepileptiform EEG does not rule out epilepsy; EEG is incompletely sensitive for epilepsy, and specialized back-averaged electromyography/EEG studies (not widely available) may sometimes be necessary to detect subtle epileptic discharges associated with negative or positive myoclonus.[4] If clozapine-induced negative myoclonus is actually an epileptic phenomenon, it might be expected to improve with certain antiepileptic medications (e.g., ethosuximide) but worsen with others (e.g., carbamazepine, phenytoin).[6]

Nonepileptic etiologies for clozapine-induced negative myoclonus must also be considered. As noted by Desarkar et al.,[1] abnormalities in neurotransmitter systems, including the orexin system known to be associated with narcoleptic cataplexy,[3] may also play a role in clozapine-induced negative myoclonus. Asterixis is also a potential explanation for Desarkar et al.'s patient, whose high serum valproate level (assuming the units were μg/ml—not μg/dl as printed) either alone or in combination with clozapine could have contributed to a subtle toxic-metabolic encephalopathy.

It is hoped that this clarification of terminology will facilitate integration of research findings from different areas of neurology (epilepsy, sleep disorders, movement disorders) to provide further insight into the pathophysiology of clozapine-induced negative myoclonus.

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