Steroid Treatment of Primary Progressive Aphasia

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Objective: To learn if oral steroid treatment can alter the signs of primary progressive aphasia (PPA). Many patients with PPA have had a vasectomy and there is a possible link between vasectomy and autoimmune diseases. If PPA is, at least in part, an autoimmune disease, patients might improve with immunosuppressant treatment.

Design: Case report.

Setting: Cognitive and memory clinic.

Patient: A 68-year-old right-handed man with a 2.5-year history of progressive speech impairment who had a vasectomy 25 years prior.

Results: Examination revealed that he had a nonfluent aphasia with intact repetition and comprehension. Before and during oral prednisone treatment, he was assessed for speech fluency, naming, and episodic and working memory. All assessments except episodic memory showed a dramatic improvement. On reassessment 1 month after discontinuing treatment, the patient's performance on cognitive testing had regressed toward baseline.

Conclusions: Although this patient's improvement with steroid treatment provides support for the postulate that PPA might be a treatable autoimmune disease, future placebo-controlled trials are needed before conclusions can be drawn.

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Primary progressive aphasia (PPA) is a progressive degenerative disorder that primarily affects language and is often included in the spectrum of frontotemporal dementias or frontotemporal lobar degenerations.1 Primary progressive aphasia was originally described by Pick2 in 1892, and more recently by Mesulam,3 who noted that there could be 2 forms, one primarily a progressive nonfluent aphasia with intact comprehension and the other, a form that presents primarily with naming and comprehension deficits. Some now term this latter form semantic dementia.4 Most patients with the nonfluent PPA have atrophy of the left inferior frontal lobe5 and can have a variety of pathological changes, including the intracellular deposition of the cytoskeletal protein tau or ubiquitin or tau-positive spherical neuronal inclusions called Pick bodies and some even show the changes associated with Alzheimer disease.1

The etiology of PPA has not been determined, but a recent study found an increased incidence of PPA in men who have undergone vasectomy.6 A link between vasectomy and PPA was postulated to be a response generated after the blood-testis barrier is broken and an autoantigen, such as tau, expressed on spermatozoa, is exposed to the immune system. If PPA was caused by an autoimmune response against brain-expressed tau protein, then suppression of the immune response may alter the course of the disease. Herein, we report the first case, to our knowledge, in which the course of PPA was altered by oral steroid therapy.

Report of a Case

A 68-year-old, right-handed retired software engineer with newly diagnosed PPA presented with a 2.5-year history of progressive difficulty expressing himself and an impairment of recent memory. He also complained of inability to manage his finances because of impaired reading comprehension. His family noted no change in his personality. His medical history was significant for a treated vitamin B12 deficiency and an episode of transient global amnesia that occurred 7 years prior to presentation. He had a vasectomy 25 years prior to presentation. His family history was significant for dementia in a maternal grandmother. He had received a steroid injection for arthritis of his shoulder 1 month prior to being seen in our Cognitive and Memory Clinic and receiving the diagnosis of PPA.
His general neurological examination revealed no evidence of parkinsonism and results were normal, with the exception of bilateral upgoing toes. Cognitive examination revealed prominent deficits in language, with a non-fluent aphasia sparing repetition. His speech was telegraphic and contained frequent semantic and phonemic paraphasic errors. Comprehension was relatively spared. He was able to understand almost all simple sentences but he did occasionally have some problems with complex commands that required superior working memory. Formal tests of working memory revealed that he was impaired (Table). Calculation, praxis, and emotional prosody were normal. Magnetic resonance imaging was performed, which revealed subtle atrophy in the perisylvian regions of the left frontal and temporal lobes.

Prior to treatment, the patient underwent 2 baseline neuropsychological examinations, separated by 1 month, using a battery of neuropsychological tests called the Florida Mental Status Examination. Informed consent from the patient was obtained. The 1-month washout period was chosen to reduce the potential for the steroid injection to confound the treatment trial for his PPA. The treatment trial consisted of 60 mg of prednisone daily. Neuropsychological testing was repeated at 1 month and again at 3 months. The prednisone dose was then tapered by 5 mg per week and the patient was reassessed 1 month after having completely discontinued treatment.

During the 2-month tests, there were many distractions and the testing was not thought to be valid. The poor performance on the serial 7s task at 3 months may not reflect a true cognitive deficit. The patient repeatedly gave “3” as the first iteration when he apparently meant “93,” but since we strictly adhered to the formal scoring criteria, he was not given credit for the response. The results of the pretreatment, treatment, and posttreatment tests are in the Table. It appears that not only was there a lack of progression of deficit, but that steroid treatment induced remarkable improvements in his impaired cognitive functions. After the treatment was discontinued, the patient’s performance regressed to his pretreatment baseline.

### Comment

The pathology seen in cortical tissue of those with PPA is primarily degenerative with a lack of inflammation. The underlying mechanism behind the degeneration remains unclear. The results of steroid treatment seen in this patient suggest the possibility that, at least in some cases, PPA may be caused by an autoimmune response. This could occur through a mechanism analogous to paraneoplastic diseases in which antigens outside the central nervous system (CNS) trigger an immune response and lead to the formation of autoantibodies that cross-react with antigens expressed in specific areas inside the CNS leading to dysfunction and eventual destruction of affected brain areas.

The formation of autoantibodies to sperm after vasectomy has been well described, with antigenic cross-reactivity between brain and sperm. Approximately two-thirds of men with vasectomy develop autoantibodies. These antibodies not only persist for years, but titers of some forms actually increase with age. A number of shared antigens have been identified, including the cytoskeletal protein tau, protamine, NS-4, and NS-6.

As mentioned, an increased incidence of PPA in men who have had vasectomy has recently been described. Although vasectomy may be a risk factor, it is probably not an absolute requirement for the development of pathology from autoantibodies to sperm antigens. Spontaneous development of antibodies has been described in both women and men. Primary progressive aphasia occurs more commonly in men, but curiously, women tend to develop a more aggressive form of the disease. It has been observed that the sera from immune infertile men, women, and men who have had a vasectomy bore a striking similarity in that they all contained antibodies that reacted with the same small subset of sperm surface proteins.

To the best of our knowledge, our case is the first in which the course of PPA has been altered by a therapy. These results give support to the idea that a neurodegenerative disease may be mediated by the immune system. Indeed, a number of recent studies have highlighted the growing body of evidence that the immune system not only plays a role in the survival of cells within the CNS, but also directly affects the function of neurons. Primary progressive aphasia is an unrelenting and progressive disease. Our patient did not show improvement before treatment and then showed fairly dramatic improvement with steroid treatment. After treatment was discontinued, this improvement was lost. We searched the literature...
and found no reports in which there was spontaneous improvement in the signs of this disease, and thus, there is a good probability that this patient’s improvement was induced by steroid treatment. Unfortunately, our data are too limited to provide firm evidence of the mechanism underlying this disorder or its treatment. For example, we cannot be certain if all the improvements were related to a placebo effect, but this report certainly suggests some exciting possibilities for further research.

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REFERENCES


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Roger N. Rosenberg, MD

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