**Background:** To our knowledge, there have been no reports on the control of central nervous system symptoms in patients with ataxia-telangiectasia.

**Objective:** To preliminarily determine the effectiveness of corticosteroid therapy on the central nervous system symptoms of a child with ataxia-telangiectasia in whom neurological signs improved when, occasionally, he was given betamethasone to treat asthmatic bronchitis attacks.

**Design:** Case report.

**Setting:** Tertiary care hospital.

**Patient:** A 3-year-old boy with the classic hallmarks and a proved molecular diagnosis of ataxia-telangiectasia.

**Interventions:** We used betamethasone, 0.1 mg/kg per 24 hours, divided every 12 hours, for 4 weeks to preliminarily determine its effectiveness on the child’s central nervous system symptoms and its safety. Methylprednisolone, 2 mg/kg per 24 hours, divided every 12 hours, was then given in an attempt to perform a long-term treatment.

**Results:** There were improvements in the child’s neurological symptoms 2 or 3 days after the beginning of the drug treatment. After 2 weeks of treatment, the improvement was dramatic: the disturbance of stance and gait was clearly reduced, and the control of the head and neck had increased, as had control of skilled movements. At 4 weeks of treatment, adverse effects mainly included increased appetite and body weight and moon face. No beneficial effect was obtained when, after 4 weeks, betamethasone was replaced with methylprednisolone. Six months later, without therapy, the child continued to experience severe signs of central nervous system impairment.

**Conclusion:** Controlled studies to better understand the most appropriate drug and therapeutic schedule are required.

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TAXIA-TELANGIECTASIA (AT) is an autosomal recessive disease, resulting from a mutation in the gene for AT protein kinase (ATM gene, chromosome 11). The spectrum of neurodegeneration, immune dysfunction, radiosensitivity, and cancer predisposition that this disease encompasses has raised the interest of the biomedical research community. Although ATM is known to be neuroprotective, the molecular mechanisms of its function in the nervous system are uncertain. Some data suggest that ATM-dependent apoptosis may be important for the elimination of neural cells that have accumulated genomic damage during development, thus preventing dysfunction of these cells later in life. We are not aware of an effective treatment for the neurological symptoms of AT. Herein, we report the dramatic improvement of ataxia following betamethasone administration.

**METHODS**

Our aim was to preliminarily determine the effectiveness of corticosteroid therapy on the central nervous system (CNS) symptoms of a child with AT. The child's parents noticed that his neurological signs improved when, occasionally, he was given betamethasone to treat asthmatic bronchitis attacks. The child underwent evaluation, which included obtaining a medical history and performing a neurological examination. A work-up, consisting of karyotype, biochemical, and metabolic evaluations to exclude inborn errors of metabolism, an evaluation of immunocompetence, brain magnetic resonance imaging, and video electroencephalography, was also performed. The diagnosis of AT was made by Western blot analysis, which was used to measure ATM protein in lysates of lymphoblastoid cell lines.

We used betamethasone, 0.1 mg/kg per 24 hours, divided every 12 hours, for 4 weeks to preliminarily determine its effectiveness on the child’s CNS symptoms and its safety. Methyl-

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percentage of total lymphocytes (CD3 = 1236 mg/dL), and a decreased ratio of T-helper cells as a percentage of total lymphocytes (CD3/CD45 = 44%; reference range, 55%-84%), a decreased ratio of T-helper cells as a percentage of total lymphocytes (CD3+CD4+ /CD45+ = 25%; reference range, 31%-60%), and an increased ratio of B lymphocytes as a percentage of total lymphocytes (CD19/CD45+ = 33%; reference range, 6%-25%). The video electroencephalographic result was normal. No beneficial effect was observed when, after 4 weeks, betamethasone was replaced with methylprednisolone, 2 mg/kg per 24 hours, divided every 12 hours, for 3 more weeks, in an attempt to perform a long-term treatment. Six months later, without therapy, the child continued to experience severe signs of CNS impairment.

**RESULTS**

Two videos (available online at: http://www.archneurol.com) summarize the principal clinical features of the child before therapy (video 1) and the results after 4 weeks of treatment with betamethasone (video 2). Clinical improvement concerning the control of CNS symptoms was impressive.

A 3-year-old boy was referred to the hospital for marked truncal ataxia. Two months before this admission, he was examined by 2 of us (L.S. and A.F.) at another hospital for ataxia and recurrent asthmatic bronchitis. During the second hospital admission, few telangiectasias were noted in the conjunctivae (Figure). He was an alert boy with an evident disturbance of stance and gait, impaired control of the head and neck, and skilled movements. Muscular tone was decreased, and deep tendon reflexes were absent. His speech was slow, with an ataxic dysarthria. He had difficulty grasping objects because of marked dysmetria. His standing was impaired because of side-to-side swaying. Instead of walking, he was compelled to run to preserve balance. In effect, the neurological disability made him seem inebriated (video 1). Because of the patient’s young age, the International Cooperative Ataxia Rating Scale score or similar quantitative or semi-quantitative clinical scores could not be obtained. The results of karyotype, biochemical, and metabolic evaluations to exclude inborn errors of metabolism, and magnetic resonance imaging results, were normal. The video electroencephalogram, during drowsiness, showed only brief discharges of spike and waves, without clinical correlations. An evaluation of immunocompetence showed the immune system was impaired with an IgG subclass deficiency (IgG2 level, 26 mg/dL; age-matched normal values for IgG2, 88-455 mg/dL), an IgA deficiency (IgA level, 52 mg/dL; age-matched normal values for IgA, 345-1236 mg/dL), and a decreased ratio of T-helper cells as a percentage of total lymphocytes (CD3+CD4+/CD45+ = 28%; reference range, 31%-60%). The level of serum α-fetoprotein was higher than normal (49.2 ng/mL; normal value, <12 ng/mL). Western blot analysis, which was used to measure ATM protein in lysates of lymphoblastoid cell lines, showed that ATM levels were undetectable.

We observed improvements in the child’s neurological symptoms 2 or 3 days after the beginning of betamethasone treatment, 0.1 mg/kg per 24 hours, divided every 12 hours. After 4 weeks of treatment, the improvement was dramatic: the disturbance of stance and gait was clearly reduced, and the control of the head and neck had increased, as had control of skilled movements. The neurological improvement was so great that the child was able to go up and down stairs (video 2). The adverse effects observed were mainly an increase in appetite and body weight (from 15.5 kg at the beginning of treatment to 19.0 kg at 4 weeks after treatment had begun), associated with a change in phenotypic appearance (moon face) (video 2). The serum α-fetoprotein level was unchanged. The immunocompetence status showed unvaried levels of immunoglobulins (hypogammaglobulinemia A and G), a decreased ratio of T lymphocytes as a percentage of total lymphocytes (CD3/CD45+ = 44%; reference range, 55%-84%), a decreased ratio of T-helper cells as a percentage of total lymphocytes (CD3+CD4+/CD45+ = 25%; reference range, 31%-60%), and an increased ratio of B lymphocytes as a percentage of total lymphocytes (CD19/CD45+ = 33%; reference range, 6%-25%). The video electroencephalographic result was normal. No beneficial effect was obtained when, after 4 weeks, betamethasone was replaced with methylprednisolone, 2 mg/kg per 24 hours, divided every 12 hours, for 3 more weeks, in an attempt to perform a long-term treatment. Six months later, without therapy, the child continued to experience severe signs of CNS impairment.

**COMMENT**

Autosomal recessive cerebellar ataxias are a heterogeneous group of rare neurological disorders involving the central and peripheral nervous systems and, in some cases, other systems and organs. Based on pathogenic mechanisms, 5 main types of autosomal recessive cerebellar ataxias may be distinguished: congenital (developmental disorder), mitochondrial ataxias, ataxias associated with metabolic disorders, ataxias associated with a DNA repair defect, and degenerative ataxia with unknown pathogenesis. Most of these cerebellar ataxias have no specific treatment, with the exception of ataxias associated with a deficiency of coenzyme Q10 and abetalipoproteinemia.3 To our knowledge, there have been no reports on the control of CNS symptoms in patients with AT. In this study, we report a dramatic reduction of neurological symptoms in AT by using betamethasone, which, among the glucocorticosteroid drugs, is most similar to dexamethasone.4 These impressive results raise at least 3 important questions: (1) Is there a plausible explanation for the effect of corticosteroid use on neurological symptoms in AT? (2) Why did methylprednisolone, another glucocorticoid, fail to produce the same beneficial effects as betamethasone? (3) Is long-term corticoste-
roid use a good option for a patient who is already immunocompromised?

With respect to the first question (Is there a plausible explanation for the effect of corticosteroids on neurological symptoms in AT?), unfortunately, we do not know the mechanism underlying this effect. However, if we were to speculate, one possible mechanism of action is interaction with specific receptor proteins in target tissues to regulate the expression of corticosteroid-responsive genes, thus affecting the types and levels of proteins synthesized in various target tissues. Another possible mechanism is prevention or suppression of inflammation. It is known that, although the use of glucocorticoids as anti-inflammatory agents does not address the underlying cause of the disease, suppression of inflammation is of enormous clinical utility and has made these drugs the most frequently prescribed agents. Similarly, glucocorticoids are of immense value in treating disease that results from undesirable immune reactions. Because the immunosuppressive and anti-inflammatory actions of glucocorticoids are intrinsically linked, many of their clinical uses are based on empirical approaches, rather than on detailed understanding of their mechanisms of action. However, despite the enormous challenges, understanding of the mechanisms by which these drugs act continues to increase. For example, discovery of interactions between the glucocorticoid receptor and transcription factors, such as activator protein 1 and nuclear factor κB, motivated their use in association with potent immunosuppressive agents (eg, cyclosporine and tacrolimus), whose receptors interact with the same transcription factors, in circumstances such as organ transplantation. This practice has enabled the use of lower doses of glucocorticoids and diminished long-term complications.

With respect to the second question (Why did methylprednisolone fail to work as well as betamethasone?), there are several possibilities to consider. One is that the anti-inflammatory potency of methylprednisolone is 5 times less than that of betamethasone (ie, 5 vs 25 ×). This difference could explain the failure of methylprednisolone to reduce neurological symptoms when used as a replacement for betamethasone in the present case. We had to switch from betamethasone to methylprednisolone, because the latter has a relatively short half-life with an “intermediate” duration of action, whereas betamethasone has a long half-life. This relatively short half-life of methylprednisolone is considered an important feature because it would result in less suppression of the hypothalamic-pituitary axis. Another reason could be the more powerful effect that betamethasone has on the CNS. There is increasing evidence that, even in equipotent doses for the glucocorticoid effect, the analogue of betamethasone, dexamethasone, has enhanced penetration of the CNS compared with prednisolone. Another possibility could be the different pathways of action of betamethasone and methylprednisolone. Previous studies with dexamethasone have demonstrated that it links with nuclear receptors in cerebellar granule cells. This is likely to be a feature of methylprednisolone; however, to our knowledge, it has not been proved. A fourth explanation could be that dexamethasone has the specific effect of increasing neuronal 5-lipoxygenase expression. This is also likely to be a feature of methylprednisolone; however, to our knowledge, it has not been proved. 5-Lipoxygenase is a key enzyme in the synthesis of inflammatory leukotrienes from arachidonic acid. Although the functional significance of increasing 5-lipoxygenase expression on the physiological and/or pathological features of the CNS remains to be fully characterized, available data suggest possible roles for the 5-lipoxygenase pathway in brain aging, neurodegeneration, seizures, synaptic activity, neurogenesis, and neurodevelopment.

The third question raised by our findings is whether long-term corticosteroid use would be a good option for a patient who is already immunocompromised. This may be the most difficult question to answer. Despite the clinical heterogeneity of AT and the fact that milder forms of the disease may exhibit slower neurological progression or later onset, it is well known that patients with AT confront not only neurological deterioration and confinement to a wheelchair but also increased susceptibility to infection and cancer (in particular, leukemia and lymphoma). Research suggests that 10% to 30% of patients with AT will develop cancer. Given this complex disease scenario, it is clearly difficult to convincingly argue for or against long-term corticosteroid therapy. Reasonably, the immunocompromised status of these patients (although the severity and nature of immune system deficiency varies from child to child) and their susceptibility to cancer are powerful factors recommending against long-term corticosteroid therapy. Conversely, and no less powerful, is the argument that given these patients’ neurological deterioration and confinement to a wheelchair from the age of 10 years, long-term corticosteroid therapy is warranted. Thus, the debate is still wide open, although “a path through the woods” has been opened.

In conclusion, despite the numerous potential adverse effects of corticosteroids, their introduction into patient care 50 years ago revolutionized the treatment of many diseases. Because of potential adverse effects, the decision to institute therapy requires careful consideration of the relative risks and benefits in each patient. To our knowledge, our experience represents the first attempt to control neurological symptoms in patients with AT with a corticosteroid. Although limited to a short period, treatment with betamethasone, an analogue of dexamethasone, was followed by positive results (ie, a dramatic decrease in CNS symptoms). Methylprednisolone gave no beneficial results. Our pilot study suggests that further studies of the cellular pathways regulated by dexamethasone analogues are required to understand whether these drugs may offer a potential treatment for the neurological symptoms of individuals with AT. Controlled studies to better understand the most appropriate drug and therapeutic schedule are also required. These studies could also be useful to better understand the physiological and/or pathological features of the CNS symptoms of these patients.

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Additional Information: Available online at http://www.archneurol.com are video 1 (patient before starting betamethasone treatment) (note the evident disturbance of stance and gait, and impaired control of the head, neck, and skilled movements) and video 2 (patient after 4 weeks of betamethasone treatment) (note that the disturbance of stance and gait has been clearly reduced, and there is increased control of the head, neck, and skilled movements, as evidenced in his ability to go up and down the stairs. In addition, note the increased body weight and the moon face.).

REFERENCES


Clarification. In the Original Contribution titled “Refractory Status Epilepticus: Effect of Treatment Aggressiveness on Prognosis” by Rossetti et al published in the November issue of the ARCHIVES (2005;62:1698-1702), on page 1701, left-hand column, the last sentence of the “EEG Suppression and Outcome” subsection of the “Results” section should have read as follows: “No patient achieved complete, sustained EEG suppression.”