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Therapeutic down-regulation of central and peripheral B-cell-activating factor (BAFF) production in pediatric opsoclonus–myoclonus syndrome

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ABSTRACT

Opsoclonus–myoclonus syndrome (OMS) is an autoimmune, paraneoplastic, central nervous system disorder, characterized by cerebrospinal fluid (CSF) B-cell expansion and various putative autoantibodies. To investigate the role of B-cell activating factor (BAFF) in OMS and the effect of disease-modifying immunotherapies used to treat it, BAFF was measured by enzyme-linked immunoadsorbent assay in the CSF and serum of 161 children with OMS and 116 pediatric controls. The mean concentration of CSF BAFF and the CSF/serum BAFF ratio were significantly higher in untreated OMS compared to neurological controls. CSF and serum BAFF levels were significantly lower in children treated with ACTH or corticosteroids, as was the CSF/serum BAFF ratio. There was a strong, negative correlation between CSF or serum BAFF levels and ACTH dose. Monthly IVIg infusions had no net impact on BAFF levels, and the combination of IVIg with ACTH or steroids did not reduce or enhance their anti-BAFF effects. These data indicate that BAFF production is increased centrally, not peripherally, in OMS, implying astrocytic over production. The novel dose-related central and peripheral anti-BAFF properties of ACTH, especially, have implications for other BAFF-related autoimmune disorders, infectious diseases, and cancers.

1. Introduction

B-cell activating factor (BAFF), a member of the tumor necrosis factor family, is a key co-stimulatory molecule for mature B-cell proliferation, survival, and homeostasis, as well as the production of Ig [1]. BAFF, also known as BLyS, TALL-1, THANK, TNFSF13B, and zTNF4 [2], was thought to be derived exclusively from activated myeloid cells. However, it is expressed by normal human brain and present in cerebrospinal fluid (CSF) and is strongly upregulated in activated astrocytes within the demyelinating lesions of multiple sclerosis [3]. Serum BAFF levels are increased in many autoimmune disorders [4], and dysregulated BAFF expression is linked to the development of autoimmune pathology [5,6]. BAFF stimulates T-cell activation, which also contributes to autoimmunity [7].

A potentially important role for cytokines like BAFF in the pathophysiology of paraneoplastic disorders is largely unexplored. Pediatric opsoclonus–myoclonus syndrome (OMS) is a catastrophic neurological disorder associated with occult neuroblastoma outside the central nervous system [8]. Even when a tumor is not found, the propensity for neuroblastoma to spontaneously regress makes a paraneoplastic etiology likely. OMS typically affects toddlers, who may lose their ability to speak, sit, or walk. Opsoclonus (chaotic involuntary eye movements), myoclonus (involuntary trembling), and ataxia (incoordination) are usually accompanied by sleeplessness, extreme irritability, and rage attacks. The course of OMS may be monophasic, but most children have chronic-relapsing remitting or progressive disease, which delimits their cognitive ability and leaves them with attention deficit disorder and other behavioral problems [9].

The purpose of this study was to measure BAFF levels in CSF and serum in OMS, and to determine the effect of conventional immunotherapy on the concentration of BAFF. In OMS, the frequency of total B-cells is increased about 5-fold in CSF, even in the absence of CSF pleocytosis [10]. Both the CD5+ (T-cell independent) and CD5− (T-cell dependent) B-cell subsets are expanded [11]. BAFF is a prime candidate for investigation because of its importance to B-cell development and maturation, and humoral immunity [1]. Although rituximab (anti-CD20) is effective at eliminating CSF B-cell expansion and reducing clinical severity [12], corticotropin (adrenocorticotropic hormone, ACTH) can induce more rapid neurological remission, more so than corticosteroids or intravenous immunoglobulins (IVIg), which are also prescribed [13]. We hypothesized that ACTH, still considered to be the 'gold standard' of therapy for OMS, might have a significant differential effect on BAFF.

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2. Methods

2.1. Study design

This was a prospective case-control study, in which all symptomatic patients were evaluated once at any stage of their illness, regardless of treatment status, as long as they meet inclusion and exclusion criteria. Comparisons were made across treatment groups, ranging from monotherapy to drug combinations. Non-OMS disease controls and healthy controls were identified for comparison with untreated and treated OMS.

2.2. OMS subjects

Approval from the Human Assurance Committee (Springfield Committee for Research Involving Human Subjects) was obtained for all aspects of this study (Protocols 00-066 and 05-118). Children with OMS were recruited through the National Pediatric Myoclonus Center, the world's largest pediatric OMS research center, from 2001 to 2007 by physician referrals and through its website www.omsusa.org. The diagnosis was confirmed by the principal investigator. Parents gave written consent for lumbar puncture, which is a routine test in the evaluation of OMS, and for participation of their child in the research study. Tumors had been resected prior to evaluation. Many of the treated patients were still having motor problems; some had primarily behavioral features of OMS. Clinical information is given in Table 1. CSF specimens were obtained from all OMS; serum samples were available from 157 of the 161.

2.3. Control subjects

'Controls' were children without OMS who were already having a lumbar puncture or blood work done as part of a diagnostic evaluation for their underlying neurological disorder, and from whom additional fluid was used for research by parental consent and patient assent if applicable. Neurological disorders included ataxia ($n = 13$), myoclonus ($n = 7$), headache ($n = 9$), epilepsy ($n = 7$), developmental delay ($n = 14$), and other disorders ($n = 16$). The clinical purpose of such lumbar punctures was to rule out infection, inflammation, central metabolic disorders, pediatric neurotransmitter disorders, or to measure CSF pressure in benign intracranial hypertension. Laboratory reports were reviewed to exclude prospective controls with fever, CSF leukocytosis, bloody CSF, abnormal CSF protein or glucose, evidence of infection or autoimmune disease, or treatment with immunotherapy, including non-steroidal anti-inflammatory drugs. CSF specimens were obtained from 62 of 66 neurological controls; serum samples were available from 47. For blood studies, there was one additional secondary control group: healthy children. For these controls, involvement was limited to a blood sample and circumscribed demographic information.

Table 1
Clinical characteristics of patients with OMS and controls

Variable	Healthy controls ($n = 50$)	Neurological controls ($n = 66$)	OMS ($n = 161$)
Age in years			
Mean ± SD	11.6 ± 5.1	7.7 ± 6.0	4.1 ± 3.7
Median ± 25%/75%	11.8 ± 7.2/17	6.4 ± 3.1/11	2.8 ± 1.9/4.4
Range	(1.8–18)	(0.16–26)	(0.89–26)
Gender			
Boys, number (%)	28 (56%)	34 (52%)	72 (45%)
Girls, number (%)	22 (44%)	32 (48%)	89 (55%)
All OMS		OMS subgroups	Number (%)
Tumor detection		Untreated (drug naive)	28 (18%)
Tumor found, number (%)	64 (40%)	ACTH-treated	31 (19%)
Tumor not found, number (%)	97 (60%)	ACTH-with-IVIg-treated	30 (19%)
OMS onset age in years, mean (range)	1.8 ± 1.1 (0.25–6.9)	Steroid-treated	11 (7%)
		Steroid-with-IVIg-treated	15 (9%)
OMS duration in years, mean (range)	2.3 ± 3.7 (0.07–25)	IVIg-treated	15 (9%)
		Previously treated	31 (19%)

2.4. Treatments

Patients with OMS either were untreated (immunotherapy naïve), were on various conventional immunotherapies, alone or in combination (Table 2), or had been treated previously but not currently. Some children were being treated with the combination of ACTH and IVIg, or steroids with IVIg. Most treated patients with OMS had been on immunotherapy for 1.4 ± 2.5 years. As expected, the mean duration of OMS was significantly longer in previously treated patients (9.5 ± 5.8 years) than in untreated (0.54 ± 5.6 years) or currently treated ones (2.0 ± 3.1 years).

2.4.1. ACTH

Those on ACTH usually had been placed on our high-dose protocol, which utilizes Acthar Gel (Questcor Pharmaceuticals, Union City, California) initially at 75 IU/m^2 body surface area by intramuscular injection twice a day for 1 week, daily for 1 week, on alternate days for 2 weeks, then tapered gradually as tolerated [14]. The mean dose of ACTH in IU/m^2/day did not differ significantly between the ACTH-only (27 ± 28) and ACTH-with-IVIg treatment groups (36 ± 27). With both groups combined ($n = 61$), the dose was administered daily in 21% and on alternate days in 79%. For statistical comparisons, the value for the alternate day dose was halved to represent the equivalent of daily dosing.

2.4.2. IVIg

Patients on IVIg typically were given 1 g/kg intravenously for 2 consecutive days at induction, then 1 g/kg monthly maintenance [13]. Among IVIg groups, there was no statistically significant difference in duration of IVIg therapy or the interval between the most recent infusion and evaluation.

2.4.3. Steroids

Treatment with the oral corticosteroids prednisone or prednisolone is standardly initiated at 2 mg/kg, then tapered as tolerated. In the steroid-treated groups combined ($n = 26$), the most commonly used steroids were prednisone (31%) and prednisolone (50%), which are dose equivalent. Of 20 children on prednisone or prednisolone daily or on alternate days, the dose was administered daily in 60% and on alternate days in 40%. There was no statistically significant difference in the dose of prednisone or prednisolone. As expected, children on daily steroids were receiving a higher dose than those tapered to alternate day dosing. Five other children, who were treated with dexamethasone ($n = 3$, prednisone-equivalent dose = 2 mg/kg) or methylprednisolone ($n = 2$, prednisone-equivalent dose = 1 mg/kg), were included in all but steroid dose analyses, so the steroid group would be more homogeneous and comparable. The dose equivalency conversion ratio was 0.75:4:5:5 for dexamethasone: methylprednisolone: prednisone: prednisolone.

2.4.4. Previously treated OMS

Patients who were previously treated but were not on immunotherapy at the time of evaluation had been off immunotherapy

Table 2
OMS treatments at time of evaluation

Treatment	Subgroup	Time on treatment (years ± SD)	Time range (min–max)	Dose/day[a] (mean ± SD)
All ACTH		1.3 ± 2.4	0.04–12	31 ± 28
	Daily dosing (n = 13)	0.80 ± 1.4	0.04–5.1	61 ± 4
	Alternate day dosing (n = 48)	1.5 ± 26	0.04–12	23 ± 15
All Steroids		1.7 ± 3.1	0.04–14	1.2 ± 1.1
	Prednisone (n = 8)	3.5 ± 4.9	0.08–14	0.81 ± 0.80
	Prednisolone (n = 13)	0.86 ± 1.5	0.04–5.0	1.1 ± 0.71
	Daily dosing (n = 12)	0.41 ± 0.42	0.04–1.3	1.4 ± 0.61
	Alternate day dosing (n = 8)	4.3 ± 4.6	0.06–14	0.32 ± 0.28
Treatment	Subgroup	Time on treatment (years ± SD)	Time range (min–max)	Time from IVIg infusion (week)
All IVIg		0.72 ± 1.1	0.02–6.0	4.2 ± 1.9
	IVIg-only (n = 15)	1.0 ± 1.7	0.02–6.0	3.8 ± 2.0
	IVIg-with-ACTH (n = 30)	0.73 ± 0.98	0.08–5.0	4.5 ± 1.8
	IVIg-with-steroid (n = 15)	0.42 ± 0.38	0.06–1.3	3.9 ± 1.7

[a] Dose is IU/m^2 for ACTH and mg/kg for steroids.

for 2.4 ± 4.9 years. Prior treatments included ACTH (n = 10), corticosteroids (n = 9), and IVIG (n = 17), given individually, or in various combinations. Of the 31 patients, 25 had been treated only with conventional agents; 6 had also received azathioprine or chemotherapy.

2.5. Lumbar punctures

Children were fasted after midnight prior to the a.m. procedure, which followed the clinical assessment, except for access to clear liquids up to 3 h before the procedure. They were deeply sedated with IV propofol after brief sevoflurane induction by an anesthesiologist in the OR [15], which obviates problems children with OMS otherwise have with sedatives [16]. Lumbar punctures were performed atraumatically in a standardized, traditional manner, using a small #22 gauge spinal needle, and were very well tolerated [17]. Approximately 1 ml of CSF and blood were obtained for BAFF assays and maintained in a −86 °C biorepository until use. CSF protein and glucose concentrations were normal. In OMS, the CSF leukocyte count was 1.6 ± 2.3 cells/cu mm (range 0–20). In neurological controls, it was 1.3 ± 1.1 (range 0–5).

2.6. Quantification of BAFF using ELISA

To measure BAFF, we used a commercial human-specific enzyme-linked immunosorbent assay (Quantikine kits, R&D Systems, Inc., Minneapolis, MN), based on the quantitative sandwich enzyme immunoassay technique, and followed the manufacturer's instructions. The ELISA assay sensitivity or mean minimal detectable dose was stated to be 3–4 pg/ml. CSF was undiluted, but serum was diluted 1:5. Samples were thawed just once before use. All samples, controls, and standards were assayed in duplicate. A standard curve was generated for each assay (Fig. 1). Each assay plate contained samples from patient controls and OMS, and the individual placing the samples had no clinical contact. Coefficients of variation fell within acceptable parameters for CSF [intra-assay 5.4% (n = 25), inter-assay 9.5% (n = 52)] and serum [intra-assay 8.3% (n = 25), inter-assay 9.9% (n = 44)]. There was no statistically significant difference in BAFF concentrations between samples obtained earlier or later in the study. The median serum BAFF level in neurological controls (1181 pg/ml) and healthy controls (1106 pg/ml) was comparable to that reported with use of the same ELISA kit (977 pg/ml) [18]. The level of CSF BAFF was about 11–13% of that in serum, which is similar to the 10% reported for adults [3].

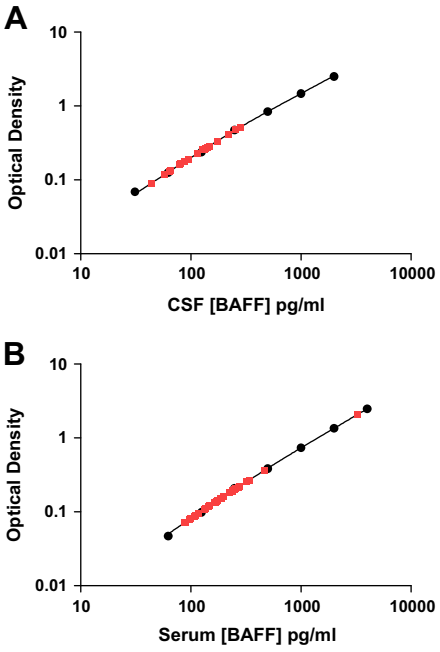

Fig. 1. ELISA assay standard curves. In these logarithmic plots for (A) CSF BAFF and (B) serum BAFF, patient data points are overlaid in red.

2.7. Statistical analysis

Statistical analysis was performed using SPSS software. Data were analyzed both as means, by analysis of variance (ANOVA) and Tukey's post hoc test for significance testing, and as medians, by Kruskal–Wallis or Mann–Whitney U tests. For the most part, means and medians were similar, unless otherwise stated. The preset level of significance for the Tukey's test was $p < 0.05$. Correlation analysis was done with Pearson correlations. Means are given with standard deviations, and medians are given with the interquartile range (25th and 75th percentiles). BAFF ratios were computed from paired CSF and blood samples.

The mean age of healthy controls, neurological controls, and OMS differed significantly, but there was no statistically significant correlation of patient age with CSF or serum BAFF levels. Excluding previously treated children, there was no significant difference in age among OMS subgroups. For those reasons, and to preserve statistical power, the groups were not age-matched. Because there was also no statistically significant correlation of gender with BAFF concentration, the data from both genders was combined. The

Table 3
Effect of OMS and immunotherapy on mean BAFF concentrations and ratios

Group	*n*	CSF	Serum	CSF/serum
Healthy controls	50	–	1085 (272)	–
Neurological controls	66	153 (72)	1214 (358)	0.13 (0.06)
Untreated OMS	28	211* (160)	1127 (325)	0.20* (0.15)
ACTH combined	61	93*,† (78)	853*,†,‡,¶ (429)	0.10† (0.06)
Steroids combined	26	106† (50)	891*,¶ (371)	0.12† (0.04)
IVIg-treated	15	149 (88)	1139 (256)	0.13 (0.07)
Previously treated	31	140† (42)	1220 (323)	0.12† (0.03)

BAFF levels are expressed as pg/ml. Standard deviations are given in parentheses. Symbols indicate statistically significant post hoc comparisons with neurological controls (*), untreated OMS (†), healthy controls (‡), and previously treated OMS (¶).

sample size of subgroups of neurological controls was too small for secondary analysis.

3. Results

3.1. CSF and serum BAFF in controls and OMS

CSF BAFF was 38% higher in untreated OMS than in neurological controls (Table 3). Heterogeneity was particularly striking in untreated OMS, with several extreme values (⩽852 pg/ml). When assays were rerun on those samples, the high values were reproduced. The median CSF BAFF concentration (182 ± 125/211 pg/ml) also was 35% higher than controls (135 ± 113/170 pg/ml). Frequency analysis showed that 68% of patients with untreated OMS had CSF BAFF levels above the control median, and 64% were above the control mean. In serum, there was good agreement between BAFF levels in healthy controls and neurological controls, but no statistically significant difference between controls and untreated OMS. In neurological controls, the mean BAFF concentration was 7.9-fold higher in serum than in CSF; the median was 8.8-fold higher.

3.2. Effect of conventional immunotherapy on CSF BAFF

There was a highly significant effect of treatment on mean ($p = 1.3 \times 10^{-6}$) and median ($p = 1.2 \times 10^{-10}$) CSF BAFF concentration (Fig. 2). Because there were no significant differences in BAFF levels between ACTH- and ACTH-with-IVIg-treated OMS, or between steroid- and steroid-with-IVIg groups, the respective groups were combined for analysis and clarity of presentation. Compared to untreated OMS, mean CSF BAFF concentration was 56% lower in the combined ACTH group ($n = 62$), and 50% lower in the combined steroid group ($n = 26$). In comparison with neurological controls, CSF BAFF was significantly lower by 39% in the ACTH group. CSF BAFF levels did not differ significantly between ACTH and steroid groups.

Monthly IVIg infusions had no statistically significant effect on CSF BAFF levels. When used adjunctively with ACTH or steroids, there was no evidence that IVIg had a synergistic effect. It did not abrogate the effect of either agent.

3.3. Effect of conventional immunotherapy on serum BAFF

There was a highly significant effect of treatment on mean ($p = 2.9 \times 10^{-6}$) and median ($p = 1.4 \times 10^{-9}$) serum BAFF concentration. Compared to untreated OMS, the mean serum BAFF level was 24% lower in the combined ACTH groups and 21% lower in the combined steroid groups. In comparison with both healthy and neurological controls, it was 21–30% less. There was no statistically significant effect of IVIg treatment.

3.4. CSF/serum BAFF ratio

CSF/serum ratios were calculated for paired CSF and serum samples and analyzed by group. Compared to neurological controls, the mean ratio was significantly higher (+54%) in untreated OMS. Some very high ratios were found in untreated OMS

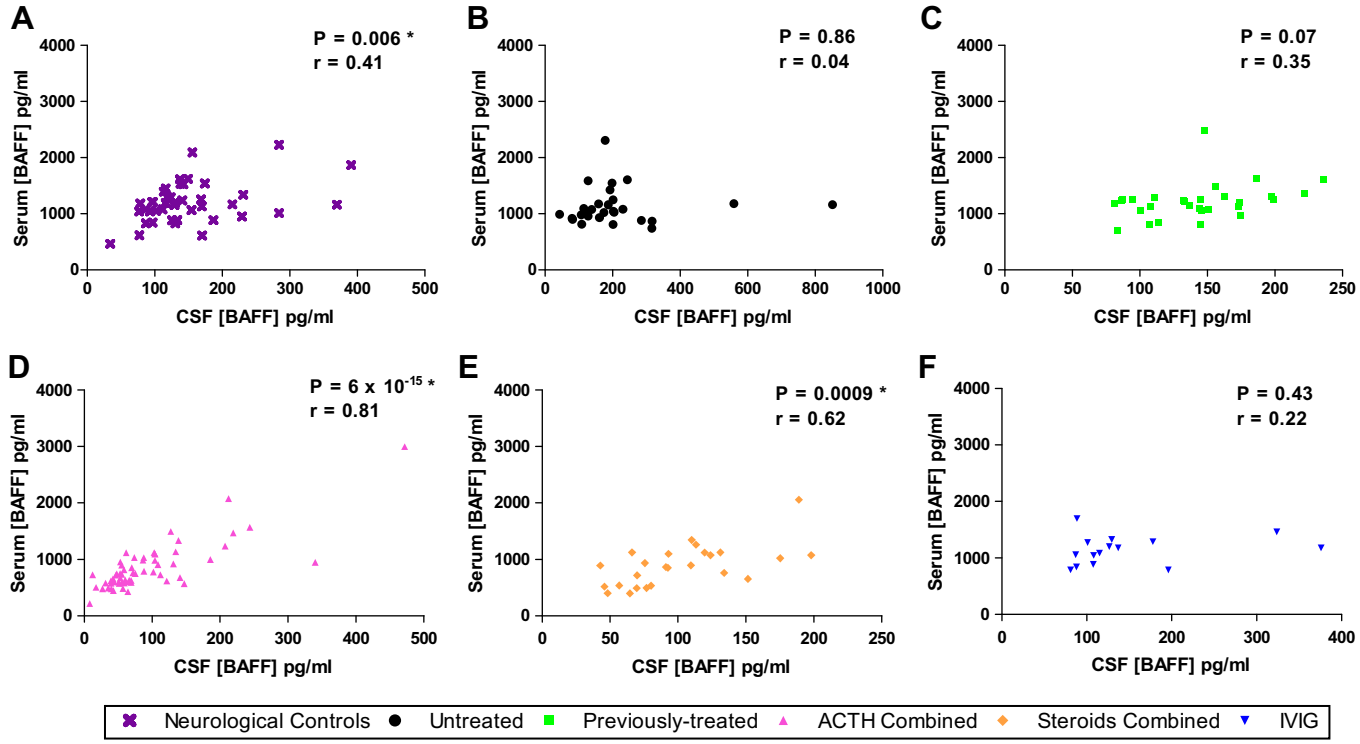

Fig. 2. Correlation of CSF and serum BAFF levels in controls and OMS not on immunotherapy (upper figures) and OMS on treatment (lower figures). Asterisk indicates statistically significant effect. The most statistically significant correlations were found in (D) ACTH- and (E) steroid-treated groups, with lesser correlations for (A) neurological controls, and none for (B) untreated OMS, (C) previously treated OMS, or (F) IVIg monotherapy.

(⩽0.73), however, the median ratio in untreated OMS (0.14 ± 0.11/0.21) also was 40% higher than in controls (0.10 ± 0.09/0.15). In comparison to untreated OMS, the mean ratio was significantly lower in combined ACTH groups (−50%), combined steroid groups (−40%), and previously treated OMS (−40%), but not in the IVIg group.

3.5. Correlation of CSF and serum BAFF

The correlation between CSF and serum BAFF levels was highly significant for the combined ACTH-treated group and moderately significant for the combined steroid-treated group (Fig. 2). In neurological controls, CSF and serum BAFF were weakly correlated. In untreated OMS, they were not correlated—the higher CSF concentrations were not matched by higher serum concentrations. They were not correlated in the IVIg group or previously treated either.

3.6. Relation of BAFF levels to ACTH dose

To analyze for a possible ACTH dose effect, correlation tests were also performed (Fig. 3 A and B). There was a significant negative correlation between CSF BAFF concentration and ACTH dose in the ACTH groups combined (graphed data), even in the ACTH monotherapy group ($r = -0.39$, $p = 0.03$) (data not shown). Serum BAFF concentration was also correlated with ACTH dose. As expected, daily ACTH dosing had greater anti-BAFF effects in CSF and serum.

3.7. Relation of BAFF levels to steroid dose

Correlation tests were run in the combined steroid groups (Fig. 3 C and D). No significant correlation was found for CSF BAFF concentration and steroid dose. There was a moderate to large negative correlation between serum BAFF levels and steroid dose.

4. Discussion

The main finding was that immunotherapy with high-dose ACTH or steroids lowered BAFF levels in CSF as well as serum in children with OMS. In the case of ACTH, the effect was highly dose-related. Data suggest that both central and peripheral mechanisms may be operative. To our knowledge, this is the first demonstration of any central anti-BAFF properties of ACTH, even steroids. Because the 'cross-sectional' aspect of the comparisons did not allow cause and effect to be established, a pilot longitudinal study of high-dose ACTH has been started.

A second observation was that the CSF BAFF concentration and CSF/serum BAFF ratio were elevated in untreated OMS. Given these abnormalities and the normalcy of serum BAFF, over-expression of BAFF in the central nervous system is the most plausible interpretation. Because BAFF is produced centrally by astrocytes [3], which are active participants in cerebral innate immunity [19], a role for reactive astrocytosis in the pathophysiology of OMS would follow. Patients with OMS do not succumb to their tumors, so direct testing of the latter will not be forthcoming. It will be important to evaluate the relation of CSF BAFF to the CSF B-cell population and autoantibodies in OMS. The immunological heterogeneity in immunotherapy-naïve OMS is similar to that found in multiple sclerosis [3]. A much larger sample size will be necessary for secondary analysis of clinical variables as a possible explanation.

Thirdly, better evidence of a dose relation was found for ACTH than steroids. Why? One could argue that a larger sample size for steroid-treated OMS might have brought out such a relation, however, the dose relation was already stronger in the size-equivalent ACTH monotherapy group ($n = 31$) than in the steroid groups

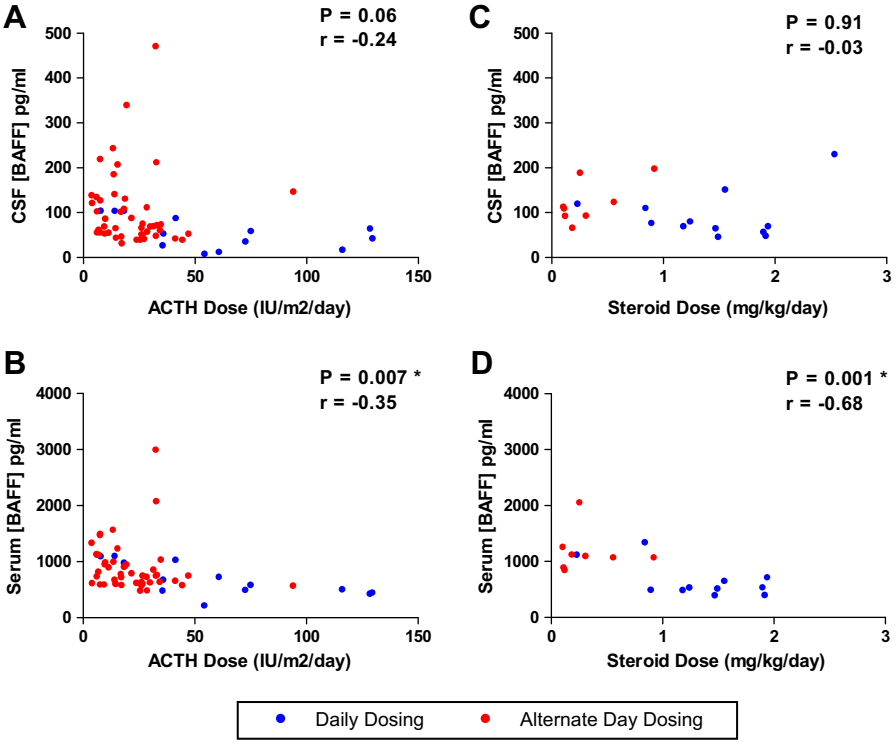

Fig. 3. Relation of CSF (A and C) and serum BAFF (B and D) concentration to ACTH dose (left figures) or steroid dose (right figures). Both ACTH-treated groups (with or without IVIg) were combined to allow sufficient datapoints for depiction of dose regimen effects. Asterisk indicates statistically significant effect. A large, statistically significant, negative correlation was found between ACTH dose and BAFF concentrations, centrally and peripherally, and between steroid dose and peripheral BAFF concentration. As anticipated, the lowest BAFF levels were found with daily dosing.

(n = 26). Alternatively, the doses of ACTH and steroids might not be comparable.

How could ACTH and steroids reduce central BAFF production by astrocytes? Separate or shared mechanisms could be postulated. ACTH binds to brain melanocortin receptors, which are found on astrocytes [20]. ACTH also is associated with a multitude of neural properties, including modulatory effects on neurotransmitter receptors, neurometabolism, and neuronal plasticity, which have been reviewed [21]. However, high-dose ACTH therapy also increases brain cortisol levels [22]. Glucocorticoids bind to glucocorticoid receptors, which also are located on astrocytes [23], as well as neurons. Besides potential effects on astrocytes, could ACTH block BAFF expression by activated macrophages and dendritic cells, which is stimulated by IFN-γ and IL-10 produced during chronic inflammation? Could the BAFF-receptor (BAFF-R), the cognate receptor for BAFF, the B-cell-maturation antigen (BCMA) receptor, or the cyclophilin-induced ligand (TACI) receptor [2,24] be modulated by ACTH or corticosteroids? These are only speculations.

The peripheral anti-BAFF property of ACTH and steroids has therapeutic implications for other autoimmune disorders. Serum BAFF is increased in certain autoimmune/allergic diseases (systemic lupus, erythematosis, Sjögren's syndrome, rheumatoid arthritis, Wegener's granulomatosis, bullous pemphigoid, asthma), infectious diseases (Epstein–Barr virus, human immunodeficiency virus, hepatitis C infection), and cancer (non-Hodgkin's lymphoma, B-cell chronic lymphocytic leukemia, Waldenströms macroglobulinemia, multiple myeloma) [7]. In these disorders, serum BAFF is increased about 2-fold [25], which likely affects peripheral B-cell survival and splenic B-cell maturation and activation [24]. It has already been shown that glucocorticoids decrease serum BAFF in Wegener's granulomatosis [26], asthma [27], idiopathic thrombocytopenic purpura [18], and chronic graft-versus-host disease [28]. Patients in some of these reports were also on other immunosuppressants, but when it could be determined, only the glucocorticoids had a significant effect on BAFF [28].

We found no effect of once monthly IVIg treatment on CSF or serum BAFF in OMS. In vitro, IVIg recognizes several cytokines, such as BAFF, and IVIg binding prevents BAFF from exerting its anti-apoptotic effect on B-cells [29]. As a result, it has been proposed that anti-BAFF IgG in IVIg might prevent the deleterious effects of BAFF in B-cell-mediated autoimmune diseases. In our study, patients were not scheduled for evaluation soon after IVIg infusions, as to avoid transient immunological effects. Therefore, we cannot attest to short-term effects of IVIg on BAFF levels; there were no long-term effects.

In summary, our findings provide three novelties: a disease mechanism for how abnormal B-cell expansion might persist in the CSF (and brain) of children with OMS, evidence that a peripherally administered hormone blocks central nervous system BAFF production, and data on pediatric CSF BAFF concentrations and CSF/serum BAFF ratios. Only ACTH and steroids, not IVIg, were effective in reducing CSF BAFF concentration. Based on data in multiple sclerosis, increased central BAFF production implicates reactive astrocytosis in the pathophysiology of OMS. These data have broad implications for other steroid- and potentially ACTH-responsive autoimmune disorders of the central nervous system, such as multiple sclerosis and lupus, in which CSF B-cells and BAFF levels are increased.

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