# The importance of adenosine deaminase in differential diagnosis of febrile seizures and seizures due to intracranial infections

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*Eighty patients aged between 3 months and 6 years who applied to hospital with seizures were included in this study. Twenty-two of them had bacterial meningitis, 11 viral meningitis, 6 tuberculous meningitis and 41 febrile seizures. Cerebrospinal fluid adenosine deaminase (ADA) values were 33.4±42.7 U/L in tuberculous meningitis, 4.50±3.18 U/L in bacterial meningitis. 1.89±1.83 U/L in febrile seizures and 1.4H1.57 U/l in viral meningitis. The ADA values of CSF in intracranial infections were higher than those of febrile seizures (p<0.05). When ADA values in bacterial meningitis were compared with those of viral meningitis, they were higher and when compared with tuberculous meningitis they were lower (p<0.001 and p<0.05, respectively). There were negative correlation between glucose levels and ADA levels of CSF and positive correlation between protein and ADA levels in bacterial and tuberculous meningitis. We inspected that this correlation was more statistically significant in the tenth day CSF values. It was concluded that CSF adenosine deaminase was an important parameter in differential diagnosis of febrile seizures and seizures due to intracranial infections. [Turk J Med Res 1993; 11(2): 82-88]*

Key Words: Cerebrospinal fluid, Adenosine deaminase, Meningitis, Convulsion

Adenosine deaminase (ADA, EC 3,5,4,4) is an enzyme which catalyses the conversion of adenosine to inosine and is released by lymphocytes and macrophages during the cellular immune response (1-4).

The early and differential diagnosis of intracranial infections is important in terms of treatment effectiveness and prognosis. Recently, although some tests are used in the early diagnosis of tuberculous meningitis (TM), those are not statisfactory in the differentiation of tuberculous meningitis from meningitis with high protein, low glucose in serebrospinal fluid and with negative culture (5-8). The increased activity of ADA in plasma and related fluids was determined in some conditions due to tuberculous, e.g, pleuritis, peritonitis, pericarditis and meningitis (1,9,10).

On the oher hand, ADA activity was found higher in intracranial infections than in control CSF (11-13). The goal of this study was to investigate the importance of ADA activity measurements in the differential diagnosis between febrile convulsion and intracranial infections, and between viral meningitis and other meningitis, eg. bacterial and tuberculous.

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## MATERIALS AND METHODS

In this study 80 patients were sampled (age range 3 months-12 years) admitted to Research Hospital, Erzurum-Turkey, between December 1989, and December 1990. Of patients 22 had bacterial meningitis (BM), 11 viral meningitis (VM), 6 tuberculous meningitis (TM), 41 febrile convulsion (FC). Lumbar puncture (LP) was performed in all patients. In patients with intracranial infections, LP was repeated. Then, CSF samples (about 1 ml) were centrifuged for 5 minutes at 3000 rpm to obtain pellet and supernatants, the supernatants were frozen and stored at —20 °C until assayed for ADA by Guisti's colorimetric method (14).

Statistical analyses were performed using the student's t-test and linear regression analyses.

## RESULTS

General properties of patients were given in Table 1. CSF protein, glucose, and ADA levels of patients with febrile convulsion in the first day and patients with intracranial infections in the first and the tenth days were shown in Table 2. CSF ADA levels were schematized (Figures 1 and 2).

**Table 1. General features of the patients**

| | Febrile Convulsion | Bacterial Meningitis | Viral Meningitis | Tuberculous Meningitis |
|---|---|---|---|---|
| No. Patients | 41 | 22 | 11 | 6 |
| Sex (M/F) | 25/16 | 12/10 | 7/4 | 3/3 |
| Age (Year) | 2.6±2.3 | 3.5±2.86 | 4.1 ±1.20 | 2.1 ±1.72 |

**Table 2.** C S F protein, glucose and **ADA** levels in patients with intracranial infections and febrile convulsions

| | | FC (n-41) x±SD | BM (n-23) x±SD | VM (n-11) x±SD | TM (n-6) x±SD | All CNS Inf (n-39) x±SD |
|---|---|---|---|---|---|---|
| protein | 1 st day | 28.5±12.1 | 86.7±46.1 | 42.5±15.8 | 134.5±52.6 | 81.6±50.0 |
| | 10th day | – | 43.6±52.9 | 33.1 ±6.72 | 83.2±31.7 | 46.7+44.3 |
| Glucose | 1 st day | 77.3±18.1 | 50.0±32.2 | 77.5±21.7 | 28.2±15.1 | 53.8±31.2 |
| | 10th day | – | 64.1 ±18.2 | 68.1 ±9.67 | 45.8±14.9 | 62.4±17.1 |
| ADA | 1st day | 1.89±1.83 | 4.50±3.18 | 1.41 ±1.57 | 33.4±42.7 | 8.10±19.2 |
| | 10th day | – | 5.98±4.16 | 2.98±2.47 | 23.6±13.5 | 7.85±9.13 |

FC: Febrile Convulsion BM: Bacterial Meningitis
VM: Viral Meningitis TM : Tuberculous Meningitis

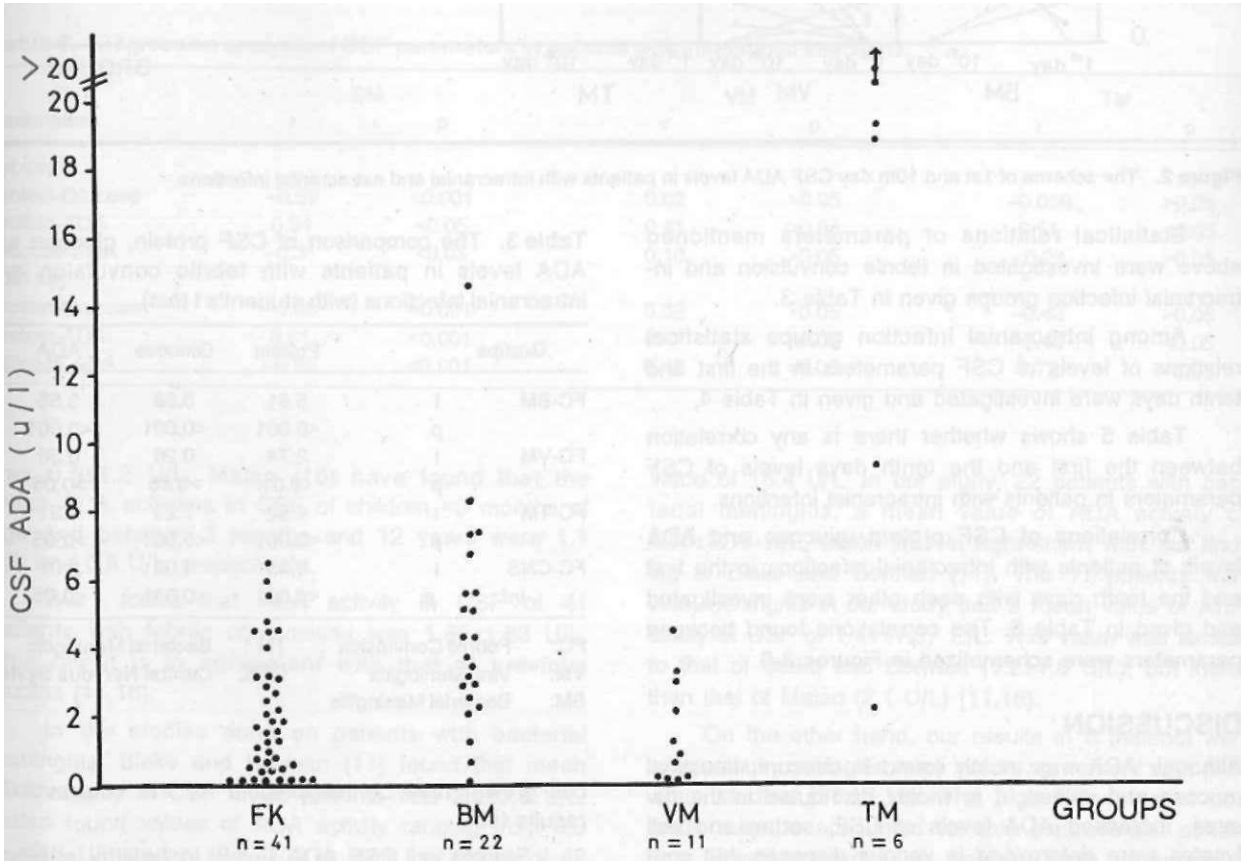



**Figure 1**. 1 st day C S F A D A concentrations in patients with intracranial and extracranial infections.

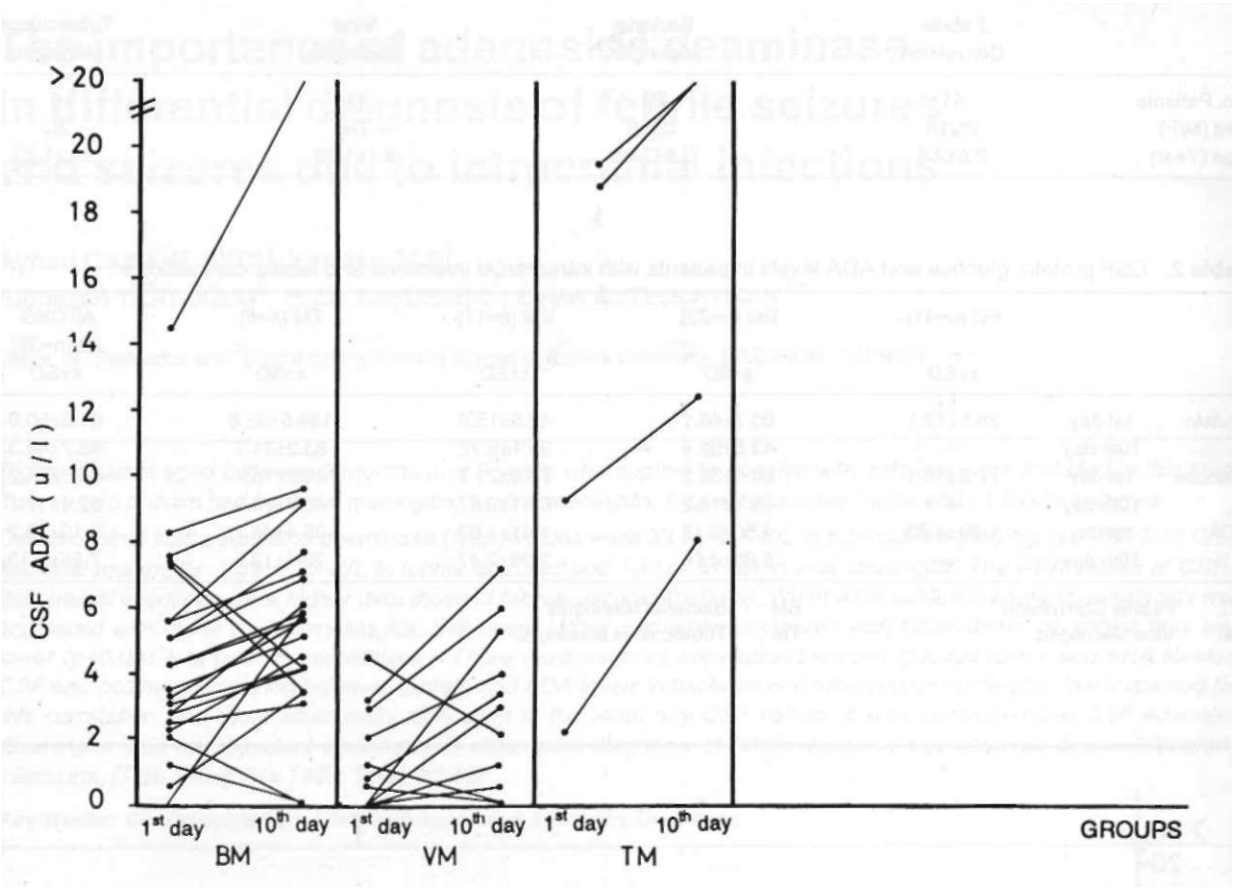



Figure 2. The scheme of 1 st and 10th day C S F ADA levels in patients with intracranial and extracranial infections.

Statistical relations of parameters mentioned above were investigated in febrile convulsion and intracranial infection groups given in Table 3.

Among intracranial infection groups statistical relations of levels of C S F parameters in the first and tenth days were investigated and given in Table 4.

Table 5 shows whether there is any correlation between the first and the tenth days levels of C S F parameters in patients with intracranial infections.

Correlations of C S F protein, glucose and A D A levels of patients with intracranial infections in the first and the tenth days with each other were investigated and given in Table 6. The correlations found between parameters were schematized in Figures 3-6.

Table 3. The comparison of C S F protein, glucose and A D A levels in patient6 with febrile convulsion and intracranial infections (with student's t test)

| Groups | | Protein | Glucose | ADA |
|---|---|---|---|---|
| FC-BM | t | 5.81 | 3.68 | 3.55 |
| | P | <0.001 | <0.001 | <0.001 |
| FC-VM | t | 2.74 | 0.26 | 0.36 |
| | P | <0.01 | >0.05 | >0.05 |
| FC-TM | t | 4.92 | 7.23 | 1.81 |
| | P | <0.001 | <0.001 | >0.05 |
| FC-CNS Inf. | t | 6.45 | 4.09 | 2.01 |
| | P | <0.001 | <0.001 | <0.05 |

FC Febrile Convulsion
VM Viral Meningitis
BM Bacterial Meningitis
TM : Bacterial Meningitis
CNS: Central Nervous System

## DISCUSSION

Although A D A was mostly found in caecum, Intestinal mucosa and spleen, it is widely distributed in the tissues. Increased A D A levels of C S F, serum and cell lysates were determined in various diseases, but controversial results were reported on this subject. That the different A D A levels occur in different stages of cell growth may be responsible for the controversial results (15).

Studies on C S F A D A levels in healthy subjects are limited. Blake and Berman (11) have reported that the mean A D A activity in C S F of 25 healthy subjects

**Table 4.** The comparison of the 1st and the 10th day CSF protein, glucose and ADA levels in intracranial infection group (with student's t test)

| Groups | Protein | | Glucose | | ADA | |
|---|---|---|---|---|---|---|
| | t | P | t | P | t | P |
| **BM1-VM1** | 4.04 | O.001 | 2.69 | <0.001 | 3.74 | <0.001 |
| **BM2-VM2** | 0.91 | >0.05 | 0.84 | >0.05 | 2.59 | <0.01 |
| **BM1-TM1** | 2.03 | <0.05 | 2.36 | <0.001 | 1.66 | <0.05 |
| **BM2-TM2** | 2.31 | <0.01 | 2.53 | <0.01 | 3.18 | <0.01 |
| **VM1-TM1** | 4.18 | <0.001 | 5.26 | <0.001 | 1.84 | >0.05 |
| **VM2-TM2** | 3.82 | <0.001 | 3.31 | <0.001 | 3.73 | <0.001 |

1:1st day 2:10th day

Table **5.** The statistical relation between the 1st and the 10th day CSF values in patients with intracranial infections (with student's t test)

| | BM | | VM | | TM | |
|---|---|---|---|---|---|---|
| | t | P | t | P | t | P |
| Protein (mg/dl) | 2.88 | <0.001 | 1.81 | >0.05 | 2.05 | >0.05 |
| Glucose (mg/dl) | 1.79 | >0.05 | 1.02 | >0.05 | 2.04 | >0.05 |
| ADA (U/L) | 1.33 | >0.05 | 1.78 | >0.05 | 0.54 | >0.05 |

BM: Bacterial Meningitis
VM: Viral Meningitis
TM: Tuberculous Meningitis

Table **6.** Regression analysis of CSF parameters in patients with intracranial infections

| Parameters | BM | | VM | | TM | |
|---|---|---|---|---|---|---|
| | r | P | r | P | r | P |
| 1st day | | | | | | |
| Protein-Glucose | -0.59 | <0.001 | 0.02 | >0.05 | -0.009 | >0.05 |
| Protein-ADA | 0.34 | <0.05 | 0.41 | >0.05 | 0.51 | <0.05 |
| Glucose-ADA | -0.31 | <0.05 | 0.10 | >0.05 | -0.29 | >0.05 |
| 10th day | | | | | | |
| Protein-Glucose | -0.60 | <0.001 | 0.32 | >0.05 | -0.43 | >0.05 |
| Protein-ADA | 0.81 | <0.001 | 0.47 | <0.05 | -0.49 | <0.05 |
| Glucose-ADA | -0.65 | <0.001 | 0.42 | >0.05 | 0.72 | <0.05 |

was 0.6±1.2 U/L. Malan (16) have found that the mean ADA activities in CSF of children <3 months of age and between 3 months and 12 years were 1.1 U/L and 0.6 U/L, respectively.

We found that ADA activity in CSF of 41 patients with febrile convulsions was 1.89±1.83 U/L. This result is in agreement with that of previous studies (11,16).

In the studies done on patients with bacterial meningitis, Blake and Berman (11) found that mean ADA activity in CSF of 28 patients was 2.6±3.9 U/L Malan found values of ADA activity ranging from 0.3 to 49.6 U/L (mean 12.5 U/L) in their first series of 42 patients with bacterial meningitis and in their second series of 50 patients with bacterial meningitis, a mean value of 15.4 U/L. In our study, 22 patients with bacterial meningitis, a mean value of ADA activity of 4.50±3.18 U/L, which was in agreement with the finding of Blake and Berman (11). The 11 patients with viral meningitis in our study had a mean value of ADA actiity in CSF of 1.41±1.57 U/L. This value was similar to that of Blake and Berman (1.2±1.8 U/L), but lower than that of Malan (2.1 U/L) (11,16).

On the other hand, our results in 6 patients with tuberculous meningitis were not in agreement with previous studies (11,13,16). The high SD value of our result may be accounted for this controversial condition. Previous reports in patients with tuberculous meningitis were 8.0±3.7 U/L (11), 14.5 U/L (13), and 13.7 U/L (16).

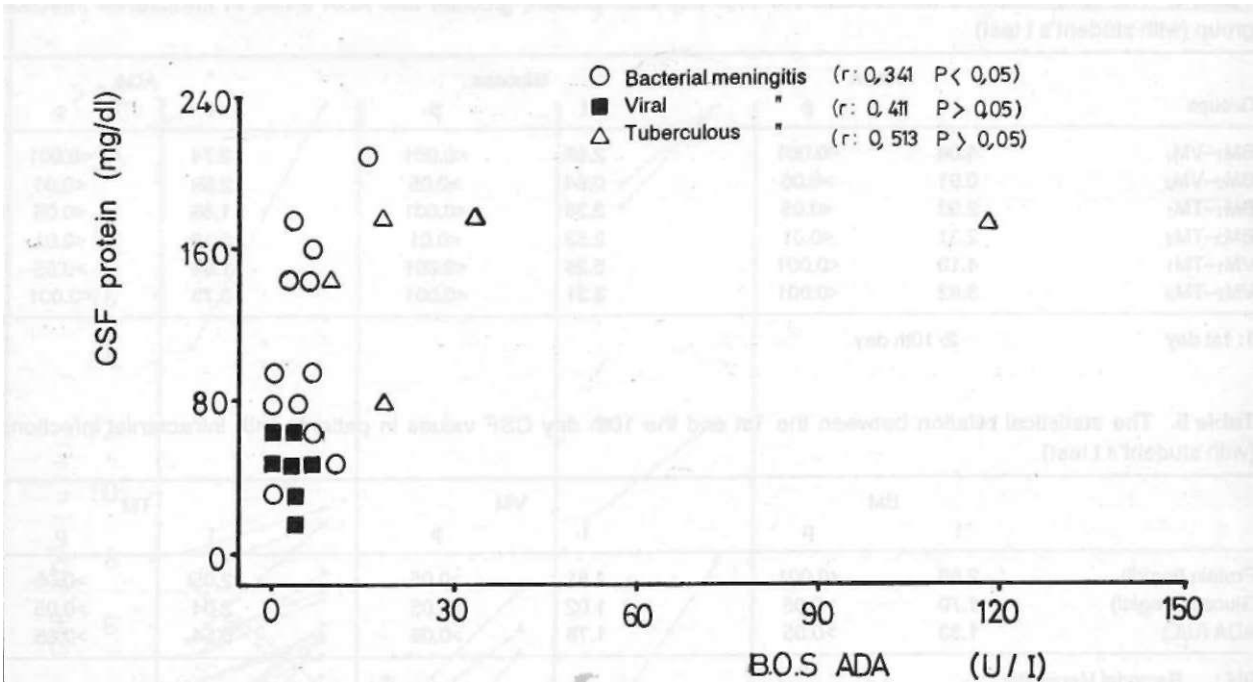



Figure 3. The correlation of 1 st day CSF ADA and protein levels in patients with intracranial infections.

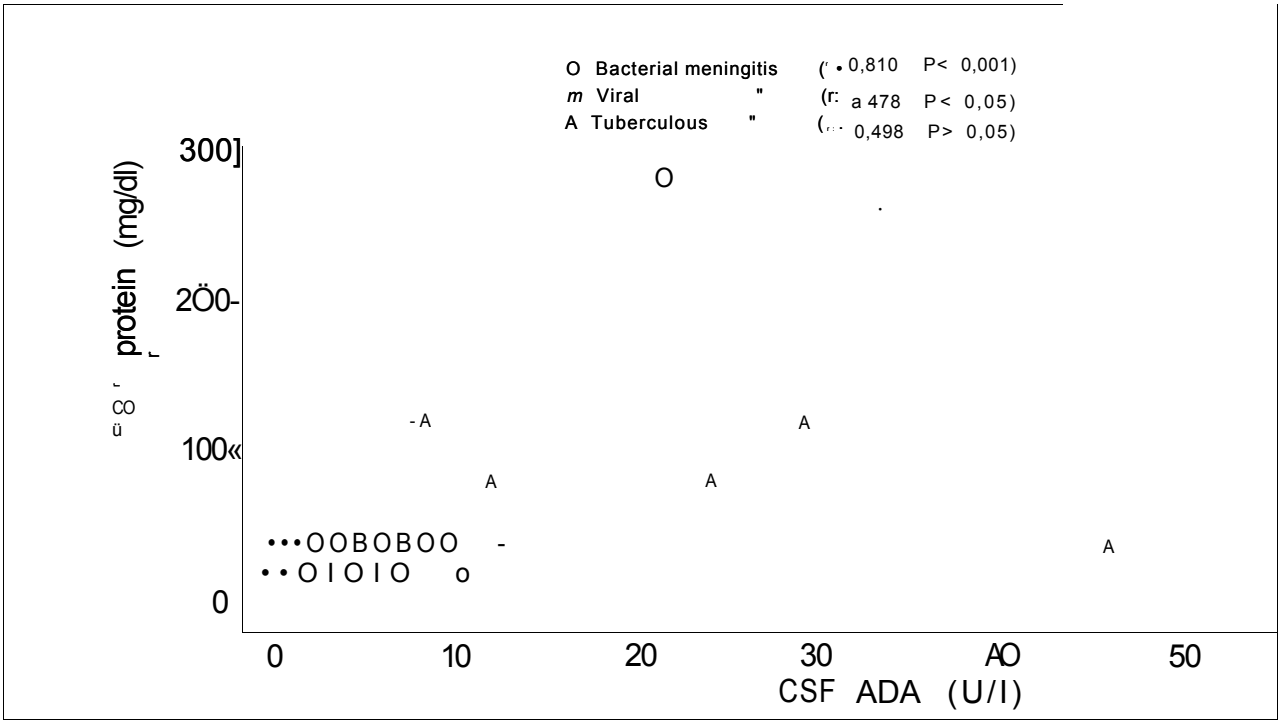



Figure 4. The correlation of 10th day CSF ADA and protein levels in patients with intracranial infections.

In the present study, ADA activity in CSF was nigher in patients with intracranial infection than those with febrile convulsions ($p<0.05$). The results is in agreement with previous studies (11,16).

Piras and Gakis (17) have reported that there was a significant difference in terms of CSF ADA activities between patients with viral and tuberculous meningitis, though there was an insignificant dif-

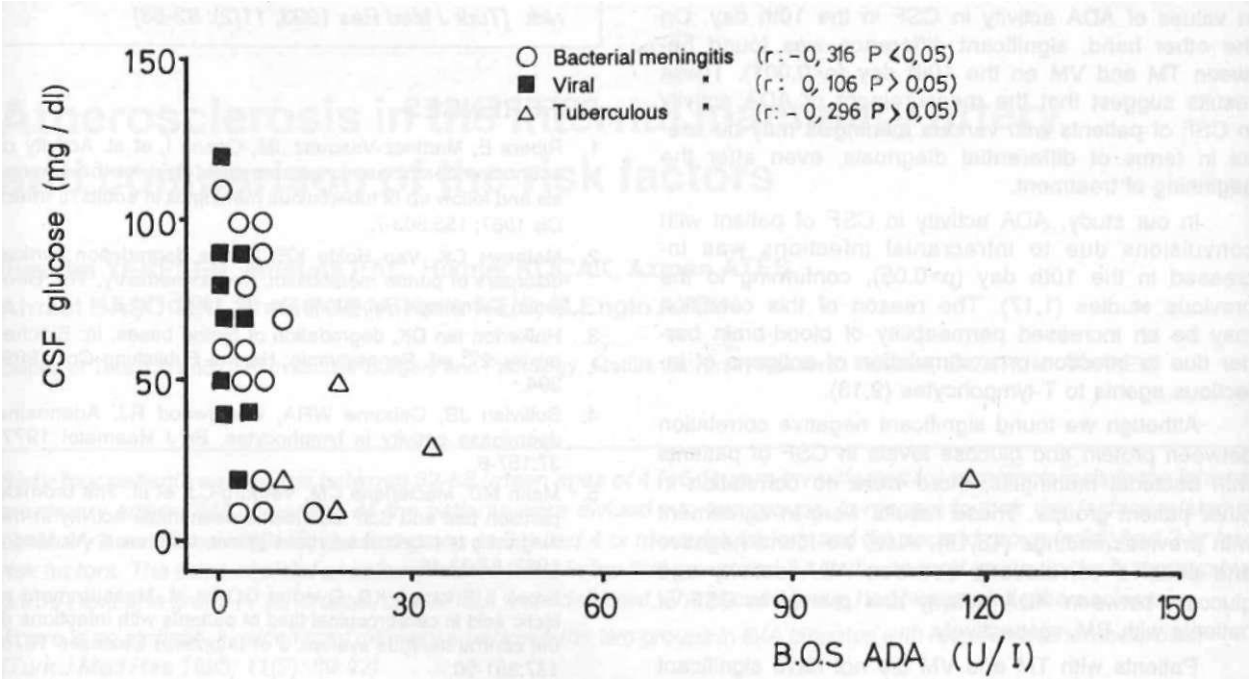



Figure 5. The correlation of 1 st day CSF ADA and glucose levels in patients with intracranial infections.

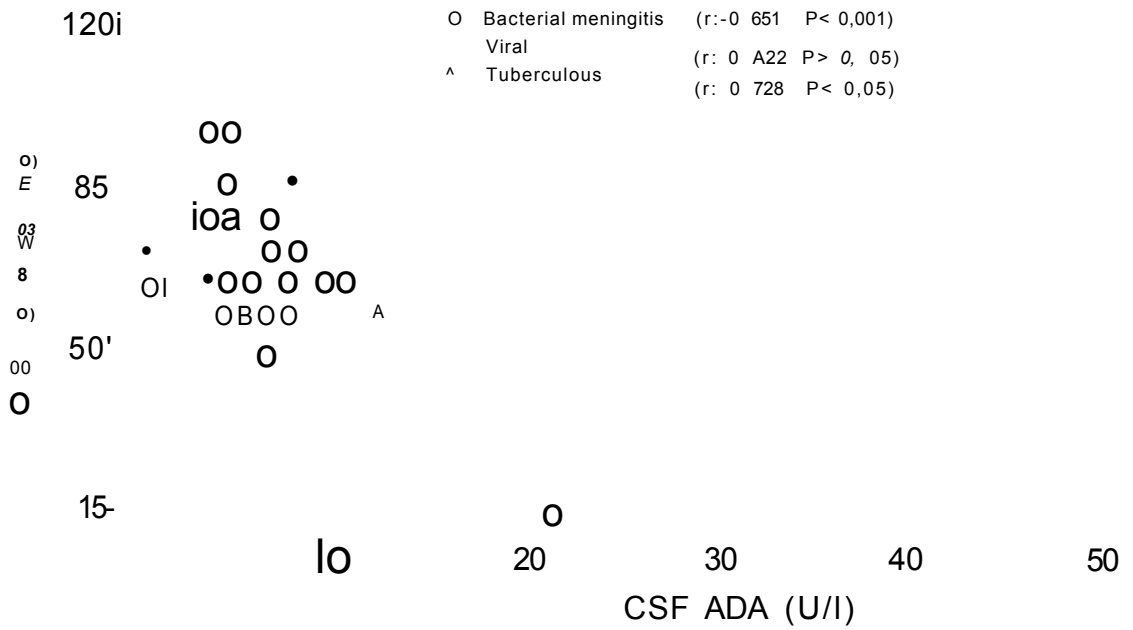
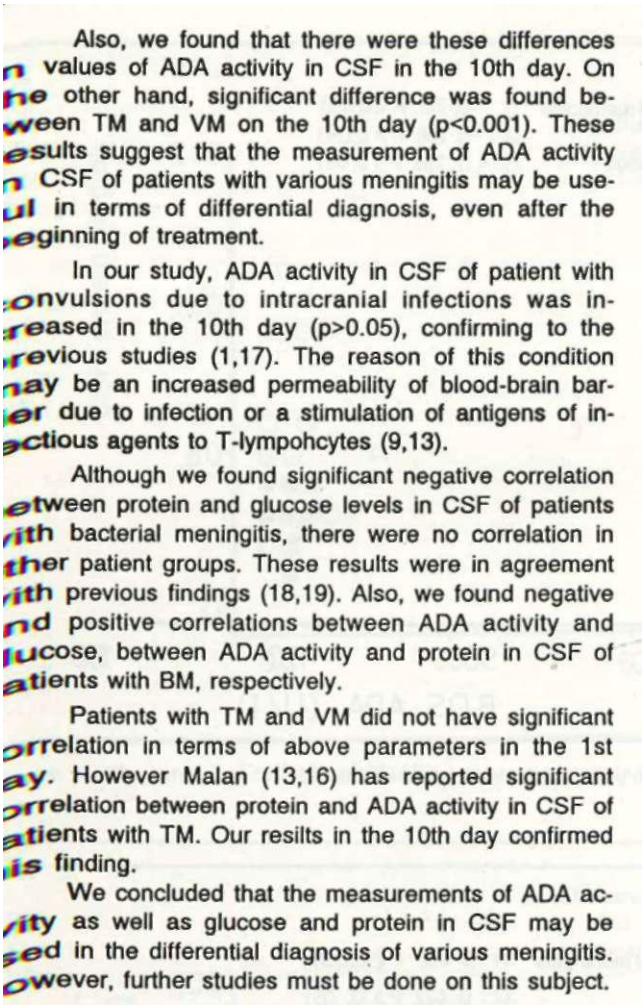



**Figure 6.** The correlation of 10th day CSF ADA and glucose levels in patients with intracranial infections.

ference in other studies (5,11,16). Our results are in agreement with the latter, because we found significant differences between tuberculous meningitis and bacterial meningitis, and bacterial meningitis and viral meningitis ($p<0.05$ and $p<0.001$, respectively) but no difference between TM and VM ($p>0.05$).



Also, we found that there were these differences n values of ADA activity in CSF in the 10th day. On he other hand, significant difference was found be- ween TM and VM on the 10th day (p<0.001). These esults suggest that the measurement of ADA activity n CSF of patients with various meningitis may be use- ul in terms of differential diagnosis, even after the eginning of treatment.

In our study, ADA activity in CSF of patient with onvulsions due to intracranial infections was in- reased in the 10th day (p>0.05), confirming to the revious studies (1,17). The reason of this condition ay be an increased permeability of blood-brain bar- er due to infection or a stimulation of antigens of in- ctious agents to T-lympohcytes (9,13).

Although we found significant negative correlation etween protein and glucose levels in CSF of patients ith bacterial meningitis, there were no correlation in ther patient groups. These results were in agreement ith previous findings (18,19). Also, we found negative nd positive correlations between ADA activity and lucose, between ADA activity and protein in CSF of atients with BM, respectively.

Patients with TM and VM did not have significant orrelation in terms of above parameters in the 1st ay. However Malan (13,16) has reported significant orrelation between protein and ADA activity in CSF of atients with TM. Our resilts in the 10th day confirmed is finding.

We concluded that the measurements of ADA ac- ity as well as glucose and protein in CSF may be ed in the differential diagnosis of various meningitis. owever, further studies must be done on this subject.

**Febril ve intrakraniyal enfeksiyonlara bağlı konvülzyonlarınayırıcıtanısındaadenozin deaminazınönemi**

*Bu çalışmaya nöbet nedeniyle hastaneye baş vuran ve yaşları 3 ay ila 6 yıl arasında değişen 80 hasta dahil edildi. Bunlardan 22'sinde bakteryel menenjit, 11 'inde vira! menenjit, 6'sında tüberküloz menenjit ve 4Tinde de febril konvülzyon vardı. BOS adenozin deaminaz (ADA) değerleri tüberküloz menenjitte 4.50±3.18 U/l, febril konvülzyonlarda 1.89±1.83 U/l ve vira! menenjitte 1.41±1.57 U/l îdi. Intrakranial enfeksiyon/ardaki BOS ADA değerleri febril konvülzyonlardaki değerlerden daha yüksekti (p<0.05). Bakteriyel menenjitteki ADA değerleri vira! menenjittekinden ise daha düşüktü (sırasıyla p<0.001 ve p<0.05). Bakteriyel ve Tüberküloz menenjitte BOS glukoz düzeyleri ile ADA düzeyleri arasında negatif korelasyon ve protein ve ADA düzeyleri arasında ise pozitif korelasyon vardı- Bu korelasyon özellikle onuncu günde istatistiksel olarak daha anlamlı idi. Sonuç olarak febril Konvülzyonların ve intrakranial enfeksiyonlara bağ// nöbetlerin ayırıcı tanısında BOS adenozin deaminazının önemli bir parametre olduğu kanaatine varıldı. [Türk J Med Res 1993; 11(2): 82-88)*

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