Serum Immunoglobulins and complement subfactors levels in sodium valproate treated epileptic patients

Dr. Imad Abdul-Jabbar Thanoon*, Omer AH Ahmed, Mohammed Khalid Al-Nori***, Nazar A-K Hami****

Departments of Pharmacology*, Surgery****, Mosul College of Medicine, Departments of Clinical Pharmacy**, biochemistry***, College of Pharmacy; University of Mosul, Iraq

Received Accepted
٢٩.٦.٢٠١٠

٢٠.١٠.٢٠١٠

ABSTRACT

Objectives: To assess, the serum levels of immunoglobulins (IgG, IgA, IgM) and complement subfactors (C٣, C٤) in newly diagnosed epileptic patients in the pre-therapy stage and ٣ months after valproate therapy, in comparison with controls.

Methods: This study was conducted at Iben-Seena Hospital and the College of Medicine- University of Mosul from January to December ٢٠٠٩. Forty-two newly diagnosed epileptic patients were selected and included in this study. Fifty apparently healthy subjects , age and sex matched to the patients group also included and taken as a control. Initially from both the patients and controls, blood samples were taken and assessment of sera levels of immunoglobulins and complement subfactors were done by single radial immuno diffusion method, using commercial kits. Then patients were put on valporate therapy for ٣ months and a blood sample were taken from the patients and assay of the same parameters mentioned above were done using the same technique and the same kits.

Results: There were insignificant differences between patients in pre-therapy stage and controls with regard serum immunoglobulin levels (and complement subfactors). Also there were insignificant differences between epileptic patients before and ٣ months after therapy with valproate .

Conclusion: valproate as an anticonvulsant have no influence on serum immunoglobulin (IgG, IgA, IgM) and complement subfactors (C٣, C٤) after ٣ months of therapy.

Key Words*:* newly diagnosed epileptic, valpropate therapy, immunoglobulin and complements subfactors levels.

الخلاصه

الاهداف: تحديد مستوى الكلوبيولينات المناعيه(IgG, IgA, IgM) وعوامل المتممات (C٣, C٤) في مصل دم مرضى الصرع قبل العلاج وبعد فترة ٣ اشهر من تعاطي عقار الفالبروات بالمقارنه مع مجموعة الضبط.

طرائق العمل: تمت هذه الدراسه في مستشفى ابن سينا وكلية الطب-جامعة الموصل للفتره من كانون ثاني الى كانون الاول من سنة ٢٠٠٩. تم اختيار ٤٢ من مرضى الصرع المشخصين حديثا. ايضا تضمنت هذه الدراسه مجموعه من ٥٠ شخصا من الاشخاص الاصحاء ظاهريا من اعمار واجناس مقاربه لمجموعة المرضى اتخذت كمجموعة ضبط. تم سحب عينة دم من مجموعتي المرضى والضبط وتم قياس مستوى الكلوبيولينات المناعيه والمتممات باستخدام عدد فحص خاصه وبطريقة الانتشار المناعي الشعاعي المنفرد. وبالنسبه لمجموعة المرضى وبعد فترة ٣ اشهر من تعاطي عقار الفالبروات تم سحب عينة دم ثانيه وقياس نفس المفردات اعلاه باستخدام نفس الطريقه ونفس عدد الفحص.

النتائج: لم يكن هنالك فرقا معنويا في مستوى الكلوبيولينات المناعيه وعوامل المتممات في مصل الدم بين مجموعة مرضى الصرع قبل العلاج ومجموعة الضبط. كذلك لم يكن هنالك فرقا معنويا في مستوى الكلوبيولينات المناعيه وعوامل المتممات انفة الذكر في مصول المرضى قبل العلاج وبعد فترة ٣ اشهر من تعاطي عقار الفالبروات.

الاستنتاج: ان عقار الفالبروات كمضاد للصرع لايحمل أي تأثير على مستوى الكلوبيولينات المناعيه وعوامل المتممات قبل وبعد العلاج لمدة ثلاثة اشهر عند مرضى الصرع وبالمقارنه مع مجموعة الضبط

Epilepsy is a common neurological problem which has occupied clinicians for many centuries[١]. However little is known about the aetiology of the disease, but among many mechanisms proposed, the immunological one have been implicated as an aetiological factor of epilepsy, especially in children with intractable epilepsy[٢]. Certain clinical studies suggested that aberrations of the immunologic system may be associated with untreated epilepsy and with the use of anticonvulsant therapies[٢,٣].

Immunoglobulin A (lgA) deficiency has been detected in up to ٢٥%of patients with epilepsy[٤], and the most frequent abnormality is a reduction in serum and salivary IgA concentration which occurs in about one-fifth of epileptic patients receiving diphenhydantoin[٥]. On the other hand, disturbances of immunoglobulin G and M (IgG, IgM) levels have also been reported, but the results are conflicting since both increased and decreased concentrations have been found[٥,٦]. The complements are cascading series of plasma enzymes and effector proteins whose function is to lyse pathogens and or target them to be phagocytized by phagocytic cells of the reticuloendothelial system[٧].

The aim of this study is to assess the immunoglobulin levels and complement subfactors in newly diagnosed epileptic patients before therapy and ٣ months after valproate therapy in comparison to control.

Patients and methods

This study was conducted from January to December ٢٠٠٩. Approval have been obtained from ethical committee (the main health centre in Mosul and Mosul College of Medicine, University of Mosul, Iraq). Patients were selected according to certain criteria.

Criteria for selection

١. Newly diagnosed patients with epilepsy (clinical diagnosis was made by neurologist).

٢. Selected for valproate monotherapy for the initial ٣ months.

٣. No coexisting renal, hepatic, thyroid dysfunction, nor diabetes or any disease of suspected immunological basis.

٤. Compliant patient.

Of the patients interviewed only ٤٨ were eligible for enrollment in the study according to the criteria mentioned above and only ٤٢ completed the study. They were ١٢ females and ٣٠ males with a mean± SD age ٢٦.٨٠ ±٥.١١ years (ranged between ١٨ and ٣٨ years). Also included (٥٠) apparently healthy subjects as a control group. They were (١٤) females and (٣٦) males with a mean±SD age ٢٧.٠٦±٥.٠٥ years (ranged between ١٨ and ٣٨ years). Initially from both the patients and controls, ٥ml venous blood samples were taken and assessment of immunoglobulin levels (IgG, IgA, IgM) and complement subfactors (C٣,C٤) were done by single radial immunodiffusion method[٨] using kits from Sanofi diagnostics Pasteur (France). For the patients group, they were put on valproate therapy in a mean±SD dose ٤٥٧.١٤±١٠٠.٣٣ mg/dL (ranged between ٤٠٠mg and ٨٠٠ mg/dl) for ٣ months, by the end of which another blood samples were taken and assessment of the same parameters mentioned above were done.

Standard statistical methods were used to determine the mean ,standard deviation (SD) and the range. Paired t-test was used to compare the results of

the patients in the pre and post-therapy stage. Unpaired t-test was used to compare the results of the patients in the pre-therapy stage and the controls. $P<٠.٠٥$ was considered to be statistically significant.

Results

There were insignificant differences between epileptic patients in the pre-therapy stage and the controls with regard serum immunoglobulin levels (IgG, IgA, IgM) and complement subfactors ($C^{٣}$,$C^{٤}$) as shown in Table ١

Table ١. Comparison of immunological classes and complement subfactors in pre-therapy epileptic patients and control.

Parameter Immunoglobulins and complements g/L	Patients pre-therapy No=٤٢ mean±SD	Controls No=٥٠ mean±SD	P value
IgG	١٠.٧٤ ± ١.١٧٤	١٠.٤٦٢ ± ١.٢٣٤	> ٠.٠٥
IgA	٢.٢٢٨ ± ٠.٢٥٤	٢.٢٠٦ ± ٠.٢٦٧	> ٠.٠٥
IgM	١.٤٩٠ ± ٠.٢١٤	١.٤٨٦ ± ٠.٢١٠	> ٠.٠٥
$C^{٣}$	٢.٠٥٧ ± ٠.١٩٦	٢.٠٤٦ ± ٠.٢٠٤	> ٠.٠٥
$C^{٤}$	٠.٣٦٥ ± ٠.٠٥٩	٠.٣٦٠ ± ٠.٠٥٢	> ٠.٠٥

There were insignificant differences between patients in the pretherapy and post-therapy stages with regard serum levels of immunoglobulin levels (IgG, IgA, IgM) and complement subfactors ($C^{٣}$,$C^{٤}$). Table (٢)

Table ٢. Comparison of immunological classes and complement subfactors in epileptic patients in the pre and post-therapy stage.

Parameter Immunoglobulins and Complements g/L	Patients pre-therapy mean±SD	Patients post-therapy stage mean±SD	P value
IgG	١٠.٧٤ ± ١.١٧٤	١٠.٨٥٧ ± ١.١٤٤	NS
IgA	٢.٢٢٨ ± ٠.٢٥٤	٢.٢٥ ± ٠.٢٠٩	NS
IgM	١.٤٩٠ ± ٠.٢١٤	١.٥٠٤ ± ٠.٢١٥	NS
$C^{٣}$	٢.٠٥٧ ± ٠.١٩٦	٢.٠٤٨ ± ٠.١٩١	NS
$C^{٤}$	٠.٣٦٥ ± ٠.٠٥٩	٠.٣٦٣ ± ٠.٠٥١	NS> ٠.٠٥

Discussion

Our study revealed insignificant differences between newly diagnosed epileptic patients before starting therapy and the control with regard serum levels of immunoglobulins (IgG, IgA, IgM) and complement subfactors (C٣,C٤), also there was insignificant differences between patients in pre-therapy and post-therapy stages with regard serum levels of immunoglobulin (IgG, IgA, IgM) and complements (C٣,C٤).

In ١٩٧٧ Joubert et al, reported that epileptic patients on valproate therapy had mean serum IgA levels significantly lower than non-users of valproate[٩]. In agreement with our study Lenti et al. evaluated serum immunoglobulins in ٢٥ epileptic children treated with anticonvulsants (carbamazepine and valproic acid), ١٧ untreated patients and ١٨ healthy subjects. The treated and untreated patients did not differ significantly from the controls with respect to the mean IgA , IgG and IgM serum levels, and concluded that there were no major changes in immune status related to clinical type of epilepsy or to carbamazepine or valproate therapy[١٠]. Bostantjopoulo et al.[١١] studied ٥٠ epileptic patients (٢٠ without medication, ١٥ on carbamazepine and ١٥ on valproic acid) and ٢٠ healthy controls. They reported that the untreated epileptic group had increased levels of IgA and IgG, patients on carbamazepine showed increased IgG and IgM levels, while patients on valproate had increased levels of IgM. Basaran et al. studied the humoral and cellular immune parameters in untreated and phenytoin or carbamazepine treated epileptic patients and noticed that patients on phenytoin had decreased serum IgA and IgG levels, while those on carbamazepine had decreased serum IgM levels and untreated epileptic showed immune profiles significantly different from healthy subjects suggesting that epilepsy per se may be associated with certain immune aberrations induced by antiepileptic drugs[١٢]. The complement system and immunoglobulins are the main components of humoral immunity . The activation of complement is known to be involved in a number of forms of cardiovascular disease, such as exacerbation of myocardial defect following ischaemic injury and may be involved in the degeneration of spontaneous atherosclerotic lesions[١٣]. This might be the first study concerning levels of complements(C٣,C٤) in epileptic patients before and after valporate therapy.

In conclusion, our study concluded that valproate as an antiepileptic drug did not have a significant effect on serum immunoglobulins (IgG, IgA, IgM) and complement subfactors (C٣,C٤) levels in epileptic patients.

References

١. Maurice V, Allan HR. Epilepsy and other seizure disorders in: Adams and Victors Principles of Neurology. Mc Graw- Hill ٢٠٠١:٣٤٩.

٢. Eeg- Olofsson O, Bergstorm T, Osterland CK, Andermann F, et al. Epilepsy etiology with special emphasis on immune dysfunction and neurovirology. Brain Dev ١٩٩٥;١٧ suppl:s٥٨-٦٠.

٣. Aarli JA. Immunological aspects of epilepsy. Brain Dev ١٩٩٣;١٥(١):٤١-٩.

٤. Bouma PA. Determining prognosis of childhood epilepsies by establishing immune abnormalities.
٥. Andersen P, Mosekildel L. Immunoglobulin levels and auto antibodies in epileptics on long term anticonvulsant therapy. Acta Med Scand ١٩٧٧;٢٠١(١-٢): ٦٩-٧٤.
٦. Aarli JA, Tonder O. Effect of antiepileptic drugs on serum and salivary IgA. Scand J Immunol ١٩٧٥;٤(٤):٣٩١-٦.
٧. Haynes BF, Fauci AS. Disorders of the immune system. In: Harrison's Principles of Internal Medicine, ١٥th ed. Braun WE, Hauser SL, Fauci AS, Longo DL, Kasper DL, Jameson JL editors. Mc Graw-Hill company. USA. PP:٣٠١-٥.
٨. Mancini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. Immunochem ١٩٦٥;٢:٢٣٥-٥٤.
٩. Joubert PH, Aucamp AK, Potgieter GM, Verster F. Epilepsy and IgA deficiency.The effect of sodium valproate. S Afr Med J ١٩٧٧;٥٢(١٦):٦٤٢-٤.
١٠. Lenti C, Masserini C, Peruzzi C, Guareschi CA. Effects of carbamazepine and valproate on immunological assessment in young epileptic patients. Ital J Neurol Sci ١٩٩١;١٢(١):٨٧-٩١.
١١. Bostantjopoulou S, Hatzizisi O, Argyropoulou O, Andreadis S, etal. Immunological parameters in patients with epilepsy. Funct Neurol ١٩٩٤;٩(١):١١-٥
١٢. Basaran I, Hincal F, Kansu E, Ciger A. Humoral and cellular immune parameters in untreated and phenytoin or carbamazepine-treated patients. Int J Immunopharmacol ١٩٩٤;١٦(١٢):١٠٧١-١٠٧٧.
١٣. Gardinali M, Conciato L, Cafaro C, Agostoni A. Complement system in coronary heart disease, A review. Immunopharmacol ١٩٩٥;٣٠:١٠٥-١٧.
Clin Neurol neurosurgery ١٩٩٢;٩٤ suppl: s٥٤-٦.