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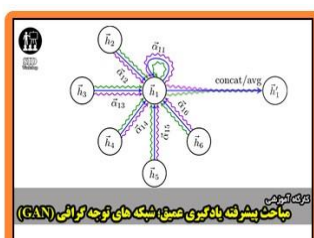


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کارگاه آنلاین کاربرد نرم افزار SPSS در پژوهش



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(Graph Attention Networks)



کارگاه آنلاین مقاله نویسی ISI و IEEE و ویژه فنی و مهندسی

RESEARCH ARTICLE

USE OF A-INTERFERON, AMANTADIN AND ISOPRINOSINE IN SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE): COMPARING THE EFFECTIVENESS

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Abstract

Objective

Sub acute Sclerosing Pan Encephalitis (SSPE), a progressive neurological disorder characterized by inflammation of the brain (encephalitis), is the result of an inappropriate immune response to the measles virus or measles vaccination. SSPE usually develops 2 to 10 years after the original viral attack. Some of the major signs and symptoms are mental deterioration, jerky movements, and seizures specially myoclonic type, involuntary movements, and/or behavioral changes, difficulty in walking, speech, and loss of cognition, respiratory distress and death.

Materials and Methods

During the ten years, from July 1991 to July 2001, we admitted 45 cases of (SSPE), at different stages of the disorder. Regardless of their stage of disease, for intervention, randomly, we used one of three drugs; Amantadin, Interferon alfa and Isoprinosine, administered to the patients, for between one month to one year. Fourteen cases received Amantadin, 15 Alfa interferon, and 16 were given Isoprinosine.

Results

While the results show all three drugs to be relatively effective, Isoprinosine showed four times more effectiveness than Amantadin and twice as much as Interferon.

Conclusion

The results showed Isoprinosine to be much more effective than Amantadin and Alfa interferon in treating the condition.

Keywords: Sub acute Sclerosing Panencephalitis, (SSPE), Dawson's disease, Slow virus diseases.

Introduction

Sub acute Sclerosing Panencephalitis (SSPE) or Dawson's disease is a rare disease of the slow virus infections group, with an onset between the ages of 7 to 10 years old approximately, presenting with a clinical picture of CNS degeneration (1).

On an average, the disorder begins 5 to 10 years after a measles infection (2). The disorder displays relatively stereotyped clinical stages, as shown in Table 1.

Alterations within the brain, usually evident on both, gross and microscopic examination (3), show sub acute encephalitis, accompanied by degeneration and

demyelination; lesions generally involve the cerebral cortex, hippocampus, thalamus and brainstem (4). In the cerebral cortex, the histologic picture is a non-specific one in sub acute encephalitis with cell loss that is sometimes accompanied by neuronophagia and meningeal reaction and predominantly CD4+ T cells, whereas the parenchyma inflammatory infiltrations are B cells (5). Inclusions are seen within both the nucleus and the cytoplasm of neurons and eosinophilic material (Cowdry type A); less often, the inclusions are small and multiple (Cowdry type B) (6). The diagnosis of measles encephalitis can be established by detecting IgG titer elevations of measles virus in acute and convalescents serum or measles – specific IgM in serum or cerebrospinal fluid (7). The measles virus also can be detected in clinical samples using the reverse transcriptase polymerase chain reaction(8,9). MRI may reveal white matter lesions compatible with acute demyelination, In SSPE, the cerebrospinal fluid, although usually normal may reveal a lymphocytosis and increase in measles antibodies (8). EEGs typically reveal myoclonic seizure or focal, generalized slowing or epileptiform discharges; CT is usually normal or shows atrophic changes, but an MRI can detect non-specific changes involving the cortex, white matter or deep nuclei (10). Paramyxovirus particles or measles virus RNA can be detected in brain tissue biopsy.

For treatment or to control disease progression, various kinds of drugs are used, such as steroids, Amantadin, α , β and γ interferon (11), transfer factor and Isoprinosine, each influencing at varying stages of the disease(12).

Materials and methods

Between July 1991 and 2001, 45 cases of SSPE, age range 3-21 years old, were admitted in the children's medical center; the mean age was 9 years old, with 32 males (71%) and 13 females (29%).

Patients were initially diagnosed based on clinical examination, and following that on the basis of the IgG titers of the serum and cerebrospinal fluid of patients; these antibody titers in the serum were between 1.64 to 1.81 fold positive, mean 1.41; for CSF they were between 1.4 to 1.102 fold positive, mean 1.51.

When initially examined at the first visit, the patients were

at different stages of the disease process; based on clinical manifestations, stages were identified by a pediatric neurologist; table 1 shows the clinical manifestations.

Classification of disease stage

Clinical signs and symptoms and EEGs were used to classify disease stages of the patients as follows:

In stage one, mental regression and behavioral alteration (aggressiveness, depression, hallucination and cognitive disorders) are prominent; main signs and symptoms observed for those in stage two are jerky movements and myoclonic epilepsy, followed by difficulty in walking and talking. In stage three patients, 3 other forms of epilepsy as generalized tonic-clonic, partial and partial complex epilepsy, choreathetic movements, disturbances of swallowing and speech were also observed, for which bed rest was advised for affected patients. Severe mental and motor deterioration, full defect in cognition, disturbances in urination and defecation and progressive respiratory infection, possibly fatal, were features observed in stage four patients (Table1).

Based on EEGs, done for all patients, of 24 cases in stages one and two, results of 15 showed typically myoclonic epilepsy, while the results of one patient demonstrated slowing and partial, or partial complex epilepsy; EEGs of the remaining patients, in stages three and four, showed severe slowing and partial epilepsy.

Twenty cases had brain CT, half of whom were in stages 1 and 2, had mild to moderate brain atrophy and the other ten cases showed brain atrophy with gliosis and demyelinating process (fig1).

Table 1: Clinical Differentiation of SSPE in different stages.

Stage 1	Stage 2	Stage 3	Stage 4
Mental deterioration Psychomotor regression Inability to have relationship Educational regression Reduction of memory Seizure	Myoclonic jerk Drop attack Choreathetosis Walking disturbances Speech disorders Psychomotor Deterioration	Reduction in Myoclonic seizures Unable to walk Other kinds of seizure Urinary and fecal incontinence Eating difficulty Respiratory distress Bed ridden Death	Completely bed rest Reduction in seizures Inability to eat Infections Heart insufficiency Respiratory insufficiency Death

Treatment

Of patients with stage one disease, 3 patients were given Amantadin, while 3 other cases received α -INF and 4 other patients took Isoprinosine; among those classified as second stage, 4 patients received Amantadin and 5 patients were administered with α -INF and Isoprinosine respectively. Stage three patients were treated with 5 patients in each group received Amantadin, Alfa interferon and Isoprinosine. Those patients with stage four of the disease were treated as follows: Amantadin with oral administration 10-15 mg/kg for 3 to 6 months, α -INF subcutaneously 3-6 million units, three times weekly for 3 months and Isoprinosine (Inosine pranobex) 100 mg/kg/day for 6 months. We followed up all patients every 2-3 months by neurological examination, EEG and psychometric tests. Patients whose follow-ups were incomplete were contacted by phone.

Definition of drugs effectiveness

Three levels of drug effectiveness were used:

1. Complete stop/cessation: Remaining at the same stage for long time after treatment or no progression to next stage of disease for at least one year or more.
2. Slow progression: This was when the progression of disease from one stage to another, lasted over two years following treatment.
3. Non-effective: If no change was observed in progression and/or deterioration in the signs and symptoms occurred, the drug was considered to be non effective.

Results

In our study, we randomly administered one of the three drugs, Amantadin, Alfa Interferon or Isoprinosine for treatment of 45 patients suffering from sub acute sclerosing panencephalitis, at different stages.

Of 14 cases treated with Amantadin, in one patient (7/15%), full cessation or “stop” of disease was seen. Three (21/5%), had slowed progression and in 10 (71/5%) cases, treatment was non effective.

In 15 cases that received subcutaneous Interferon alfa, 2 (13/33%) had complete stop of disease progression, 5 cases (33/33%), had slowed progression and in 8 patients (53/33%), the treatment was non-effective.

Of the 16 patients receiving Isoprinosine, in 4 (25%), disease progression stopped, 6 (37/5%) exhibited slow progression, and in 6 other patients (37/5%), the drug had no effect or was non-effective.

Six patients showed no response to drug treatment; two of these died within a year of admission, three of them died within two years, and the third lived for over two years.

Of the 3 cases that showed slowed progress with Amantadin, 2 lived for between two to three years, while the third survived for over 3 years.

From among 5 patients that had slow progression following Interferon alfa therapy, two died between 2 to 3 years after admission, whereas 3 lived for between 3 to 5 years following hospitalization.

Of six patients that had slow disease progression, using Isoprinosine, 3 lived for up to 4 years after admission, 2 for up to 7 years, while one lived for ten years after treatment (Table 2).

While the results show all three drugs to be relatively effective, Isoprinosine showed four times more effectiveness than Amantadin and twice as much as Interferon (Fig 2).

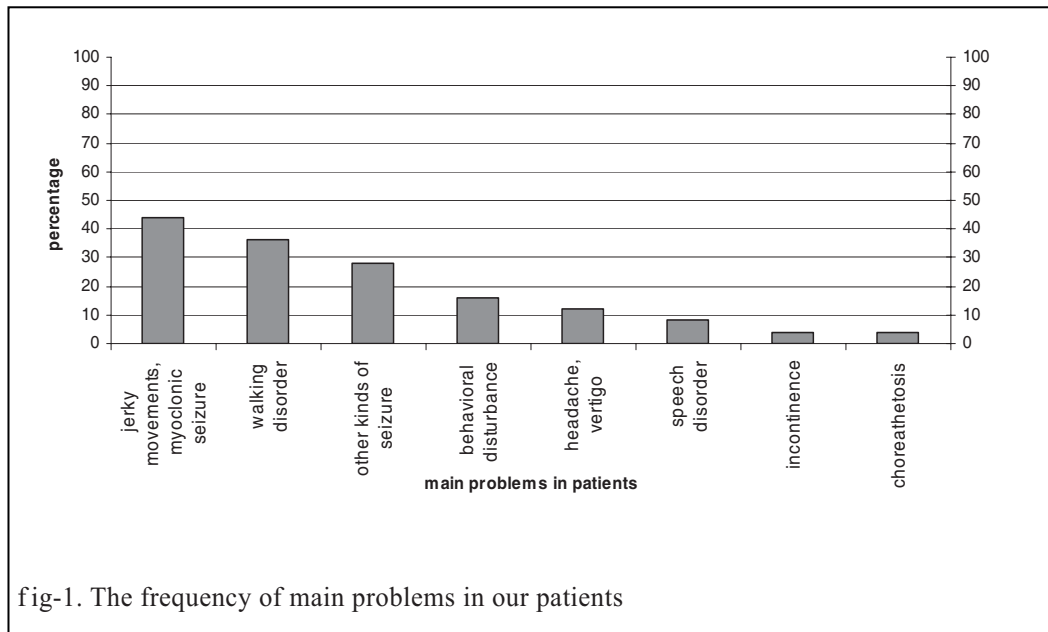


Table 2: The effects of drugs used in our patients

Drug used for one year	stage1	Stage2	Stage3	Stage4
	10cases	14cases	15case	6cases
Amantadin	3cases: Complete stop in one case Slowed progression in 1 case Non effective in 1 case	4cases: Slowed progression in 1 case Non affective in 3 cases	5cases: Slowed progression in 1 case Non affective in 4 cases	2cases: Non effect
Alfa Interferon	3cases: Complete stop in 1 case Slow progression in 1 case Non affective in 1 case	5cases: Complete stop in 1 case Slowed progression in 2 case Non affective in 2 cases	5case: Slow progression in 1case Non effective in 4 cases	2case: Non effect
Isoprinosin	4cases: Complete stop in 2 case Slowed progression in 1 case Non effect in one case	5cases: Complete stop in 2 cases Slowed progression in 2 cases Non effect in 1 case	5case: Slowed progression in 3 cases Non effect in 2 cases	2case: Non effect

Discussion

Sub acute sclerosing panencephalitis is a degenerative disease that caused by measles virus that initially produces an acute measles infection or immunization after routine vaccination (13). The measles virus normally has 7 kinds of protein that body produce specific antibodies against that proteins; however in some patients there is defective antibody production for the M particle of the measles protein that influences virus invasion of the cells and the brain and produoce destruction of neurons .In children and young adult within 2 to 10 years, many of the neurons begin to degenerate, causing progressive

deterioration of the functioning of the cortex, sub cortical tissues, spongy degeneration in cortico- sub cortical regions, cerebellum and the brainstem may be seen(14). This process is accompanied by increases of the measles antibody in the CSF and the patient's blood, as seen in our patients(15).

Various kinds of drugs are used to control disease progression and some of these can have temporary side-effects (10). In this study we found out that the best result is obtained using Isoprinosine in comparison to the other drugs investigated; the mean survival rate of 6 years was documented for Isoprinosine users, in comparison with 4 and 3.33 years for those administered α -INF and Amantadin respectively. A 1997 study showed that, in patients treated with intra ventricular α -INF and oral Inosiplex, the survival was between 9 to 54 months (mean 2.83 years); although the effect of α -INF is limited, they found it to be most efficient therapeutic agent in treatment of SSPE (10). In another study, a case report, the patient after combination of α -INF, Ribavirin and Inosiplex therapy improved between 6 months to 10 months, but then his condition suddenly deteriorated and he died (15). However in our study we demonstrated that complete stop (25%) and slow progression (37.5%) were found in the Isoprinosine group.

Because of the limited numbers of patients, the statistical test did not show any significant differences between our three groups (p -value >0.05), but the results can definitely show the efficacy of Isoprinosine, on disease progression and patient survival, in comparison with two other drugs. Anlar and Coworkers recommend intraventricular Interferon and oral Isoprinosine, especially for those with slow progressive disease; this can produce longer life expectancy (16).

A multi national trial indicated that approximately 35% of patients with SSPE stabilize during Inosine pronabex, whereas they had no added benefit from interferon alfa (17)Some patients have improved or stabilized after several 6-week of treatment with interaventriculr alpha interferon, starting at 105 inosine probex (Isoprinosine), 100mg/kg/day, courses which can be repeated six times at 2 to 6 month intervals(18).

Clonazepam, sodium valproate and some time

cabamazpine are effective in controlling myoclonic jerks and other type of seizures (19).

Conclusion

Although all three drugs were found to be relatively effective, Isoprinosine showed four times more effectiveness than Amantadin and twice as much as Interferon.

Because of the chronic and progressive nature of SSPE and similarity of clinical manifestations after treatment with spontaneous remissions, further long term studies are strongly recommended to investigate drug effectiveness for the appropriate treatment this disease

References

1. Bergamini F, Defanti CA, Frante P. Subacute sclerosing panencepalitis: a reappraisal. New york: Elsevier. 1986. P.440
2. Ohya T, Martinez AJ, Jabbour JT, Lemmi H, Duenas DA. Subacute sclerosing panencephalitis: correlation of clinical, neurophysiologic and neuropathology finding. NEUROLOGY 1974; 24:211
3. Dawson JR Jr. Cellular inclusions in cerebral lesion of epidemic encephalitis. Arch Neurol Psychiatr 1934; 31:685-700.
4. Herndon RM, Rubenstein LT. Light and electron microscopy observation on the development of viral particles in the inclusions of Dawson's encephalitis (SSPE). Neurology 1969; 18:8-20.
5. Hirano A, Wang H, Gombart AF, Wong TC. The matrix proteins of neurovirulent sub acute sclerosing panencephalitis virus and its acute measles progenitor are functionally different. Proc Natl Acad Sci USA 1992; 89:8745-8749.
6. Schmid A, Spielhofer P, Cattaneo R, Bacsko K, Termeulen V, Billeter MA. Sub acute sclerosing panencephalitis is typically characterized by alterations in the fusion protein cytoplasmic domain of the persisting measles virus. Virology 1992; 188(22):910-915.
7. Mehta PD, Thormar H, Wisniewski HM, Patric BA. Oligoclonal IgG bands with and without measles antibody activity in sera of patients with sub acute sclerosing panencephalitis (SSPE). J Immunol 1982; 129(5): 1983-1985.

8. Miller C, Farmington CP, Harbert K, the epidemiology of(SSPE)in England and Waes1970-1989.Int J Epidemiol 1992; 21:998-1006.
9. Honarmand S, Glaser Ca, Chow E, Sejvar JJ., Preas CP, Cosentino GC, et al. Subacute sclerosing panencephalitis in the differential diagnosis of encephalitis .Neurology 2004; 63:1489
10. Anlar B, Yalaz K, Oktem F, Kose G. Long-term follow-up of patients with (SSPE) treated with intraventricular Gama-interferon . Neurology 1997; 48(2):526-528
11. Du Rant Rh, Dyken Pr.The effect of Inosiplex on the survival of (sspe).Neurology 1983;33:1053-1055.
12. Gascon GG. International consortium on sub acute sclerosing panencephalitis .Randomized treatment study of Inosiplex versus combined Inosiplex and intraventricular interferon-alpha in sub acute sclerosing panencepaliths (SSPE): International multicenter study. Child Neurol 2003; 18(12): 819-827.
13. Hayashi T.; Ichiyama T.; Nishikawa M.; Furukawa S. Carbamazepine and myoclonus in (SSPE).Pediatr Neurol 1996 May; 14(4):346.
14. Pe Bento R, Naqui SH, Arca MM,et al. fulminating sub acute sclerosing panencephalitis:case report and literature review .Cli Pediatr1997; 149-154.
15. Freman TM. The clinical spectrum and early diagnosis of Dawson's encephalitis .J child neurol1991; 6:146-149.
16. Anlar B, Saatci I Kose Get al.MRI findings in(SSPE) Neurology 1996; 47:1278-1283.
17. Yagi S Misury,Kataoka n,et al.The origin of myoculous and periodic synchronous discharges in(SSEP).Acta Paedhtr Jpn.
18. Kenet F. Swaiman, Stephen Ashwal, Donoferriero. Peditric neurology:principles and practice.Philadephia 2006 page 1617-1618.
19. Gerald M.Fenichel.Clinical pediatric neurology,A Signs and Symptoms Approach Fifth Edition 2005:page142.

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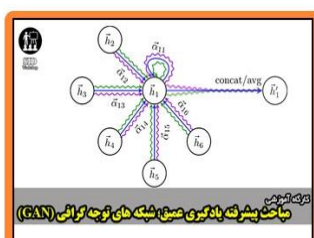
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کارگاه های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی



آموزش آنلاین ابزار پژوهش کمی (کاربره نرم افزار SPSS)

کارگاه آنلاین کاربرد نرم افزار SPSS در پژوهش



مباحث پیشرفته یادگیری عمیق شبکه های توجه گرافی (GAN)

مباحث پیشرفته یادگیری عمیق؛ شبکه های توجه گرافی (Graph Attention Networks)



مقاله نویسی ISI (روزه علمی مهندسی)

کارگاه آنلاین مقاله نویسی IEEE و ISI ویژه فنی و مهندسی