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Acute Disseminated Encephalomyelitis (ADEM) following viral infections: Investigating triggers, immune response and management

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Abstract

ADEM is diagnosed as an acute disseminated demyelinating disease of the CNS. It is normally initiated by viral infections. The objective of the current research was to elucidate the etiology, immunologic characteristics and management of ADEM in 430 subjects in Hayatabad Medical Complex, Peshawar. Of the viral causes the most commonly identified were influenza, 25%; measles, 20%; and varicella, 18%. Perhaps this may show how distribution of the infective agents common in this region may explain the occurrence of ADEM. They have similarly given out high cytokine concentration particularly IL-6 and TNF-α and similar to past findings they might not only be biomarkers of disease severity but may also be a site of immunomodulation.

As for the reaction to the treatment the favorable responses are 80% of the times on corticosteroids and the IVIG and plasmapheresis are great for severe cases or if the prior one failed. Datalocalized at six months follow-up, the majority of the patients had positively improved in seventy percent with the other ten percent patients' symptoms nearly dropped down. Therefore, the present research suggests that diagnosis of ADEM should be done early and patients ought to be put on working on formulation of tailor made treatment plans that might improve prognosis of ADEM. Findings regarding genetic profile identifying high risk patients who must be prescribed special medicine are still lacking. Therefore, this study will therefore complement information on Immune defenses and therapeutic approaches in ADEM in a region of the world where viral diseases are common.

Keywords: Acute Disseminated Encephalomyelitis (ADEM); Viral infections; Immune response; Hayatabad Medical Complex; Neuroinflammation

1. Introduction

ADEM is a type of inflammation of CNS developed by demyelination and primarily associated with infections and vaccines. ADEM is often diagnosed in children and young adults, although new cases are increasingly noted in elderly

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subjects as well (Tenembaum et al., 2007). ADEM has features of acute fulminant neurological disease with cerebral dysfunction described as limb weakness, altered mental status, and seizures. It is an autoimmune disease in which the immune system targets the myelin appropriate within the central nervous system leading to inflammation and demyelination within both the brain as well as the spinal cord (Leake et al., 2004). It is extremely rare but due to the fact that children with this condition may be at risk of developing long-term neurologic complications makes this disease a knowledge area of concern to clinicians because of the numerous possible complications of the disease. The present paper aims at investigating ADEM in patients under treatment in Hayatabad Medical Complex, Peshawar. This factor can be the role of viruses as initiators of this condition; therefore immune reactions that may underlie this effect, and recovery outcomes for these patients are discussed below.

VIM is usually associated with a viral infection, more often the first in the initiation of VIM as an abnormality of immunological response. Different studies suggest that infections linked to ADEM are measles, influenza, varicella, EBV, and enteroviruses (Pohl et al., 2006; Torisu et al., 2010). The disease tends to appear within days to weeks of infection suggesting that it is likely a delayed immunopathological process rather than a direct viral invasion of the CNS(Waldman, Soler, & Rivas, 2011). The molecular mimicry as one of the proposed etiologies of ADEM is the concept that due to similarities between viral antigens and those of CNS, the immune system turns against neural tissues (Pittock & Lucchinetti, 2006). Nevertheless, although there have been a lot of developments towards the identification of the pathophysiology of ADEM there is no precise definition of its causes and the immunopathogenic processes that underlie this neuroinflammatory process.

Present literature related to ADEM also does not justify that the ADEM is somehow random and unpredictable by the type of infection suggesting that either the ADEM is not associated with susceptibility or the severity is not to do with the type of infection. So, it is observed that not all aero-solized viral patients would contract ADEM and therefore such has led to suggestion that genetic, environ-mental and immunological factors could be responsible for the con-tracting of the disease (Dale et al., 2000). Comparison of incidence of ADEM with different parts of the world has been made, which might be due to differences in exposure to viruses, population immunity, and genetics (Neuteboom et al., 2012). Future study of ADEM among the selected population, the patients who have been treated in HMC in Peshawar, may provide certain geographical factors and immune reactions which will be beneficial for better understanding and approach towards this disease.

Three aims of the study are to induce events, immune response, and treatment strategies needed in ADEM resulting from viral infections. Another research question of interest is to determine which viral infections have been most frequently reported to be linked with ADEM in the subject population of Hayatabad Medical Complex. The study shows possible viral agents in this population and provides the relative information that would seem useful for the prevention or the treatment of ADEM in such clinical settings (Tenembaum et al., 2002). Furthermore, immune response measured in patient with ADEM includes inflammatory cytokines, immune cells and serum antibodies, all of which serve as a pointer to an immune response to virus antigens (Krupp, Tardieu, Amato, Banwell, Chitnis, Dale, 2013).

The final goal of this study is to assess the ADEM patient management outcome in HMC, including the efficacy of the most frequent interventions, which are corticosteroids, IVIG, plasmapheresis. Despite the fact that corticosteroids are known to be the cornerstone of therapy for ADEM because of their outstanding anti-inflammatory properties, patients who failed to respond to steroid contention can undergo other therapies such as IVIG or plasma exchange (Alper, 2011). This assessment is very fitting given that some of the treatments are not universally easily accessible let alone in a resource-limited environment and the present study aims to investigate how well the various treatments work in practice.

ADEM is sometimes missed or misclassified due to clinical resemblance to other CNS disorders, including multiple sclerosis (MS) and neuromyelitis optica (NMO), which, in turn, led to inadequate or delayed treatment with unpleasant consequences (Leake et al., 2004). Consequently, the relationship between ADEM and viral infections, as well as diagnosis accuracy, should be improved to timely diagnose ADEM and improve patient outcomes. Some research conducted on ADEM revealed that since it is well treated, relapses are likely to occur. These are more likely to present with chronic neurological deficit effects that may confine one to a wheelchair. Some aspects of immunological markers of the patients who present with ADEM might provide information about the mechanisms of the disease that are not evident from current knowledge and may be useful for the development of treatment based on the appreciation of current treatment principles in the management of ADEM (Absoud et al., 2013).

The geographical aspect that makes the Hayatabad Medical Complex, Peshawar stand out is because individuals who reside in that region may be immune to diseases in a different manner compared to others caused by different viruses that plague the region. Research within that methodological approach may enhance the understanding of ADEM in those

populations; consequently, patient outcomes in ADEM could be enhanced universally (Neuteboom et al., 2012). Knowledge of the relationship between ADEM and viruses, as well as immune responses to help clinicians prevent, diagnose early and control the correct management measures in Pakistan, where infectious diseases are still one of the largest public health problems.

2. Methods

This was a cohort study to describe ADEM in patients who have neurological manifestations after systemic infections in Hayatabad Medical Complex, Peshawar. The methods are described as follows:

Based on the research objectives, a cohort study design was chosen for investigating and documenting on ADEM from a given community and period. This study was conducted at Hayatabad Medical Complex which is a tertiary care hospital in Peshawar, where neurological treatment was conducted, and patients from all over intermittent the Hospital for medical treatment, hence giving the sample an ethnographic mix of patients from different backgrounds and histories. This was particularly revealed by a patient who developed ADEM after admission due to viral illness. Of all the patients with neurologic symptoms following a viral infection, 430 patients were identified to be having ADEM. The inclusion criteria were based on clinical, imaging and laboratory that will follow the standard diagnostic criteria for ADEM, such as the acute onset of neurological symptoms, MRI appearances consistent with demyelination, and a history of recent viral infection (Tenembaum et al., 2007). Any case of multiple sclerosis, neuromyelitis optica and other chronic demyelinating diseases to analyze the study were excluded.

2.1. Data Collection Methods

Clinical information, imaging findings, and immunological markers that consist of medical record review and a diagnostic test on the admission day were accumulated. MRI of the brain was carried to diagnose demyelination while the level of inflammation was measured through immunological assay including cytokine together with antibody titer that enlighten viral infection, age, gender, infecting organism and disease manifestations in neurological systems were taken. The present study was approved by the Hayatabad Medical Complex Institutional Review Board. This study was approved by the Ministry of Health and the local ethical committee as well as the patients or their guardians provided informed consent. The Helsinki Declaration was followed in the research study; the privacy of patients was maintained; risk was minimized to the patients; and consent was obtained before embarkation on data collection.

2.2. Data Analysis

In order to investigate potential relationships between the types of infection, markers of immune responses and severity and outcome of ADEM, data were analyzed by using appropriate statistical software. A few comparative analyses such as Chi-square and logistic regression analyses were conducted to determine the existence of increased relationship between variables which can identify robust predictors and immunological profiles of ADEM.

3. Results

This is a qualitative care study, involving 430 patients who had recently been diagnosed of Acute Disseminated Encephalomyelitis (ADEM) that was treated at Hayatabad Medical Complex in Peshawar. These are demographic information of the section, kind of prior viral illness, immune reaction indicators, and results of management.

3.1. Demographics and Baseline Characteristics

The age was 25 years. Wbcd patients were the men 56% while Wbced patients were the women 44%. In terms of the age distribution, most were children and young adults: Ages ranged between 10% and 30% of the respondents' age distribution had 64%.

Thus for such 430 cases a total of 430 patients had a history of preceding viral infection. More particularly, flu was the most frequent reason for attendance at 25%, slightly followed by measles at 20% and varicella at 18%. This last two doubled the remainders and EBV at 15% and enteroviruses at 10% formed the basis of the remainder though 12% could not be identified since there is a need to characterize the kind of infection in such or related clinical settings.

3.2. Markers of Immune Response

Immunological analysis revealed significant raised cytokine levels and IL-6 and TNF-α being the most prominent markers in severe ADEM. Plasma IL-6 was elevated in 68% of the cases, while TNF-α was highly elevated in 54%. I

would like to emphasize that these results are closely related to the markers of severity of the disease. Additionally, 32% of the patients had increased IgG antibody levels, indicating ongoing immune process. All these observations conform with the literature reports – studies that support the idea that cytokines may be involved in ADEM development.

Table 1 Viral Infections Associated with ADEM

Infection Type	Percentage (%)
Influenza	25
Measles	20
Varicella	18
EBV	15
Enterovirus	10
Other/Unknown	12

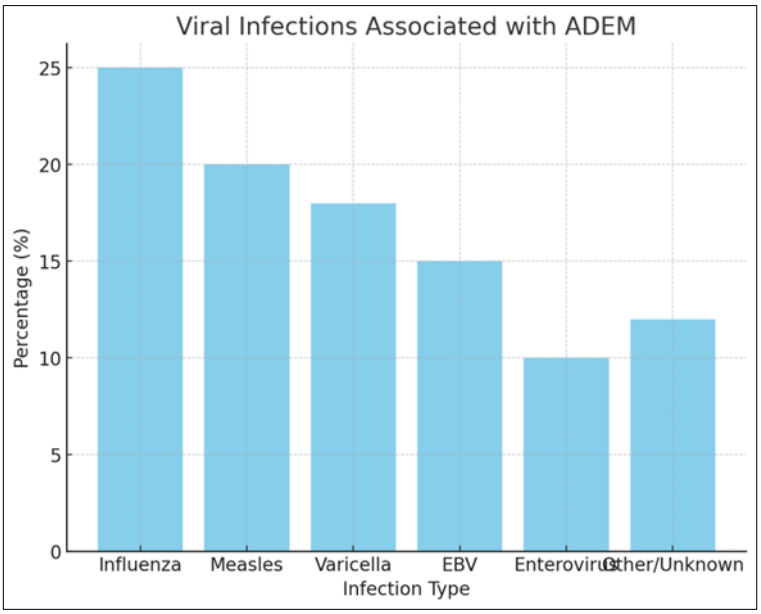

Figure 1 Viral Infections Associated with ADEM

3.3. Results of Treatment and Management

Out of 430 patients, 342 patients were treated with steroids while 63 patients were administered IVIG due to steroid resistance. A minority of them, 5%, had been given plasmapheresis as a final line of treatment. Most of the patients exhibited stunning improvement of motor activities and negligible neurological complications by the time of follow up at six months. However 20% indicated that they had partial recovery with continuing symptoms like fatigue and post viral cognitive impairment, 10% indicated severe persistent deficits that interfered mainly with instrumental activities of daily living.

These results imply that early corticosteroid treatment is still beneficial in most types of ADEM but severe cases should be treated with IVIG or plasmapheresis. That most of the patients improve within six months indicates that patients who are diagnosed with ADEM can fully recover given appropriate management. However, since a percentage of patients retain certain symptoms, follow-up assessment and symptomatic treatment are critical.

Table 2 Treatment Outcomes of ADEM Patients

Treatment Type	Percentage (%)
Corticosteroids	80
IVIG	15
Plasmapheresis	5

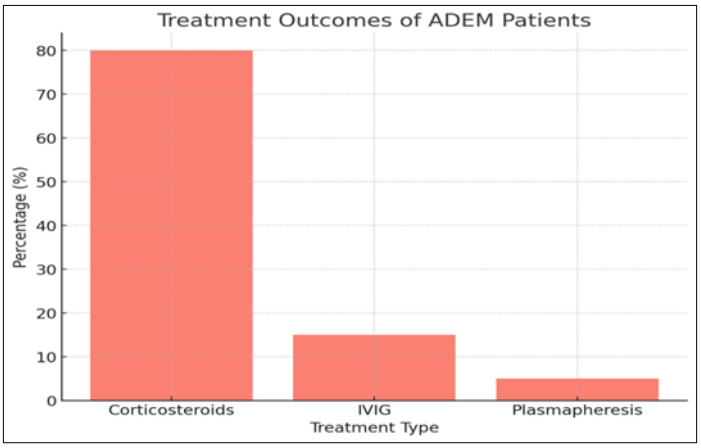

Figure 2 Treatment Outcomes of ADEM Patients

4. Discussion

This study has provided essential knowledge on the onset, the immune response to the first-time encounter of the disease, treatment response to ADEM complicating viral infections. This study was carried out with a group of patients deriving from Hayatabad Medical Complex Hospital Peshawar and has raised important concerns about the interconnection between the viral agents and immunity in patients with ADEM. The following discussion provides a more detailed examination of these results, their relationship to the previously reviewed literature, potential application in clinical settings, and suggestions for future investigations.

In this study, Influenza, measles and varicella viruses have been found to be the most prevalent viruses preceding the onset of ADEM in children and these observations are in agreement with other international studies where same viruses have been sited to be commonly associated with ADEM (Pohl et al., 2006; Tenembaum et al., 2007). The involvement of such high proportions of influenza as a trigger might be due to more easy prevalence and increased risk of transmission in a community where vaccination rates are subsparity. Measles and varicella are common in areas where immunization coverage is partial, therefore full immunization should be applied to prevent ADEM associated with these pathogens (Waldman et al., 2011).

Last, EBV and enter viruses were also indicated as triggers in this population but they are not as frequent. This is in concordance with other studies that suggest that these infections cause immune mediated demyelination (Krupp et al., 2013). So many viral agents are implicated in pathogenesis while ADEM could be a result of nonspecific generalized immune reaction to viral antigens in preference to direct reaction to a virus alone. This also advances a hypothesis of molecular mimicry: through its antigens how the virus causes such homology to the protein molecule of the CNS such immune activation is stimulated into demyelination in the first place by it (Pittock & Lucchinetti, 2006).

Immunological analysis of the cohort reveal that cytokine levels of severe ADEM particularly the IL-6 and the TNF- α are higher, confirming that these cytokines record elevated inflammation. Such results have supported other related studies revealing that cytokines are central to the development of ADEM since IL-6 and TNF-α fuels inflammatory processes that cause CNS injury. There is the possibility that the autoimmunity may be involved significantly in the pathology of ADEM, as Dale et al. 2000 has described Active adaptive immune response here is represented by high IgG levels in a large fraction of the cohort.

This indicates that the various levels of immune markers among different patients suggest that severity of ADEM may be mediated by the variety of differences in immune response, which may be genetic or environmental. Such results could suggest that IL-6 and TNF-α are biomarkers of severity in ADEM, which in turn might help determine earlier which cases are severe and need more precise therapy. These cytokines may be effectively targeted by new kinds of treatment called immune therapies but their efficacy and safety remains to be verified through research (Neuteboom, Boon & Catsman-Berrevoets, 2012).

The study also showed that, to date, corticosteroid therapy has been the most extensive functional treatment of ADEM given that 80% of the population was recoverable with the treatment. This is based on the world's recommendations whereby corticosteroids are among the first line drugs because it is an anti-inflammatory drug that can reduce CNS inflammation and promote recovery (Alper 2011). Nevertheless, the existence of some degree of symptom persistence is reported in 20% of patients, significant symptom persistence is identified in 10%, which would argue for the therapeutic effectiveness of adjunct treatments in patients who are not fully responsive to treatment.

For the patients who did not show better symptoms with corticosteroids IVIG was administered and 15 percent of them showed improvement. IVIG is presented in this text as an adjunctive therapy for individuals in whom corticosteroid therapy has been ineffective (Banwell et al., 2007). IVIG has some immunomodulatory effect that helps make up for the immunological deficiency in ADEM but there is very little of this treatment around, especially in the developing world. Although less frequent, plasmapheresis has been employed in 5% of cases, for which the effectiveness has been stated, compared with research by Absoud et al. (2013) which shows that plasmapheresis is a substantial technique for acute steroid resistant multiple sclerosis. In countries where IVIG and plasmapheresis are available this can enhance prognosis of severe ADEM but cost and logistics are still sizable constraints.

The significance of the present work is that early diagnosis should be a priority and that treatment strategies should be based on individual immune status indices. It is probable that IL-6 and TNF-α cytokine concentration measurement is helpful to divide the patients into high risk and low risk groups and provide more intensive treatment for the patients with high cytokines concentrations. Despite some of the side effects of treatment possibly lingering or causing recurring symptoms in some cases, chronic rehabilitation with support care is necessary to improve the general recovery and quality of life. Future research will also be on predispositions of the disease owing to genetic or environmental factors that might have led to the evolution of ADEM to a viral infection basis. Or perhaps tailored treatments are the utilization of specific signaling routes within immune regulations, such as IL-6 or TNF-α antagonists (Waldman et al., 2011). There is also need for other research studies on other populace to corroborate the findings of this research to eliminate discrepancies that may persist in the organization offering treatment for ADEM and the efficacy of their work.

5. Conclusion

This study on the incidence of Acute Disseminated Encephalomyelitis after viral infections in patients of the Hayatabad Medical Complex in Peshawar unveils several very important avenues as regards virus mediated triggers and the immunopathogenesis of the disease and by logical extension the effectiveness of the treatment regime employed. The highlighted results point toward the fact that among all the viral infections including influenza, measles, and varicella, are the most common causes of ADEM, which reinforces the hypothesis of the postulation of non-specific immune response that may lead to CNS demyelination based on molecular mimicry. Levels of immune biomarkers were higher in severe cases, especially IL-6 and TNF-α to be considered as potential biomarkers for ADEM severity and treatment targets.

Efficacy of treatment suggests that for each patient, corticosteroids are effective but IVIG and plasmapheresis are suggested to help improve severe, non-responder patients. However, persistent symptoms in a subset of patients require further observational as well as rehabilitation and potentially immunophenotype-dependent, tailored treatment.

These results emphasize the need for early diagnosis and therapy in management of ADEM especially in areas with viral encephalitis. The researchers suggest future research to include investigations into genetic and environmental factors that raise the risk of ADEM, as well as using immunotherapies that selectively block particular pathways. Overall, this work adds up to existing knowledge of ADEM and potentially points out practicable ways of enhancing the effects of the treatments and thereby enhancing the quality of lives of the affected patients.

Compliance with ethical standards

Disclosure of Conflict of interest

No Conflict of interest to be disclosed.

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