NEUROPSYCHIATRIC COMPLICATIONS OF ORGAN TRANSPLANTATION

by
AYMAN EMAM HASSANEIN

to be presented to

AIN SHAMS UNIVERSITY
FACULTY OF MEDICINE

Thesis submitted
in partial fulfilment of the requirement
of M. Sc. Degree
in NEUROPSYCHIATRY

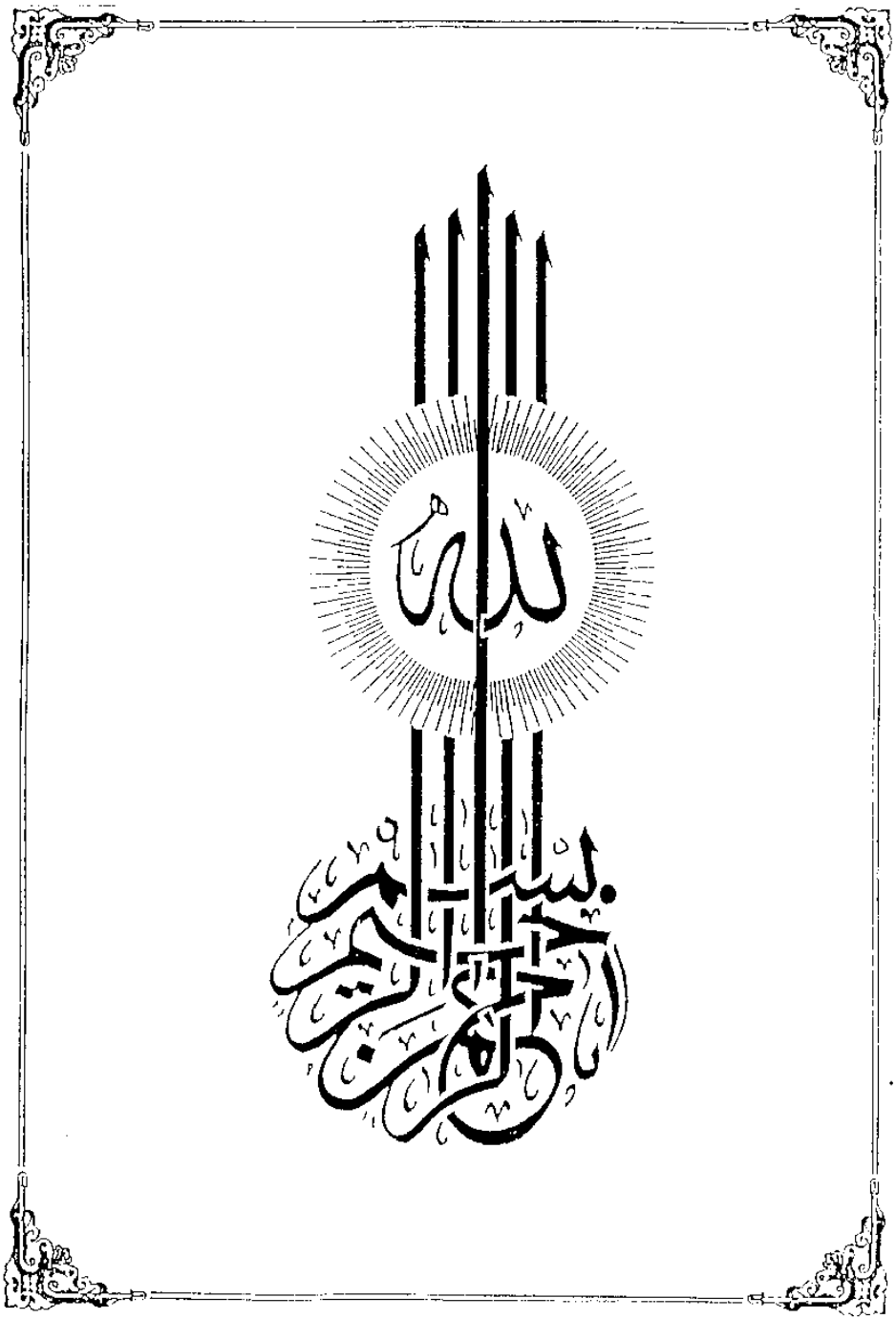
supervised by

PROF. DR. MAHMOUD MOHAMED MOSTAFA
Prof. of Neurology
Department of Neuropsychiatry
Ain Shams University

PROF. DR. MOSTAFA KAMEL ISMAIL
Prof. of Psychiatry
Department of Neuropsychiatry
Ain Shams University

1989

TO MY FATHER IN LAW



CONTENTS

ACKNOWLEDGEMENT

I would like to express my deep appreciation and extreme indebtedness to Prof. Dr. Mahmoud Mostafa, proffessor of neurology, for his well known generosity in providing the most recent references, and for his personal enthusiasm, continuous support and assurance.

Next, I wish to express appreciation and gratitude to Prof. Dr. Mostafa Kamel, proffessor of psychiatry, for his enthusiastic encouragement and sincere efforts.

I would like also to thank Prof. Dr. Emad Fadli, proffessor of neurology and head of neuropsychiatric department, and Prof. Dr. Ahmed Okasha, proffessor of psychiatry and head of psychiatric unit, for their well known support not only for me, but for every junior staff in the department.

I am deeply indebted to Dr. Tarek Asaad, and Dr. Hany Aref, who revised the manuscript and gave their comments and advice that made the work more organized and meaningful.

Also, my thanks go to all the staff of neuropsychiatric department, Ain Shams University, for their sincere desire to help me in the accomplishment of this thesis. Especially I would like to thank Dr. Magd Zakaria, and Dr. Yasser Metwally.

INTRODUCTION

It is now almost 3 decades since the first organ transplantation was performed. That interval has seen the pendulum swing from an initial flush of enthusiasm to a negative reaction associated with the high mortality rate owing to graft rejection. More recently, interest has resurged because of the development of the antirejection agent cyclosporine. This has led to rapid expansion of transplant units throughout the world, and the number of transplants now being performed is limited only by the shortage of potential donors.

However, these advances has not been without cost. Transplant recipients are subjected to numerous iatrogenic disorders, many of which involve the CNS. Neurologic complications occur in over half of all organ transplants and are frequently life threatening. The cause of neurologic complications following organ transplantation can conveniently be grouped into 4 main types: 1) complications related to the underlying disease, 2) problems resulting from the transplant procedure itself, 3) side effects of immunosuppression, and 4) post-transplant disorders peculiar to the specific type of transplant. These individual categories may assume greater or lesser importance depending on the specific transplant type involved. For example, the transplant procedure itself is one of the most common causes of neurologic complications following cardiac transplantation but not following bone marrow transplantation.

Psychological factors before and after organ transplantation have to be considered. Psychiatric manifestations of organ

transplantation may be a continuation or an aggravation of preexisting disorders. It may be caused by certain factors during the surgical procedure of transplantation, as a result of physical insult to the CNS, or due to the effect of certain drugs commonly used with this patients' population. Psychosocial stressors and fear of graft rejection also elicit concerns about the compliance after transplantation.

Previous studies have showed the important role of neuropsychiatric management, which if properly dealt with, may improve the outcome of organ transplantation.

AIM OF THE WORK

To review the neuropsychiatric complications of organ transplantation especially kidney, heart, liver, pancreas, and bone marrow, in order to:

A) Clarify their neuropathogenesis and psychopathogenesis.

B) Search for their possible management.

١٤

NEUROLOGIC COMPLICATIONS

INFECTION OF THE CENTRAL NERVOUS SYSTEM IN TRANSPLANT RECIPIENTS

Central nervous system (CNS) infection is a not uncommon cause of life-threatening infection in organ transplant recipients, occurring in 5 to 10 % of transplant patients at some time in their post-transplant course. The mortality rate of such CNS infections is high, with 44 to 77 % of immunocompromised individuals dying as a direct result of these infections (Conti & Rubin,1988). Sadly, many of these patients would have had years of productive life had their infections been prevented or treated effectively. This excessive mortality results at least in part from delays in diagnosis caused by the characteristics of these infections. The list of potential microbial pathogens is large, including pathogens commonly affecting the normal host as well as more opportunistic pathogens affecting predominantly these compromised hosts. The clinical presentation may be extremely subtle, owing to the host's impaired inflammatory response. Multiple organ systems are commonly involved and multiple microbial agents may be present, either simultaneously or sequentially. Because survival is directly related to the rapidity with which the diagnosis is made and therapy instituted, guidelines are necessary to improve the care of this problem. The purpose of this review is to provide such guidelines, based in large part upon the following factors: the patient's net state of immunsuppression, the time-table according to which different infections present post-transplant, the presenting clinical syndrome and its rate of progression, and the results of physical examination, lumbar puncture, and such imaging techniques as the computerized

tomographic (CT) and magnetic resonance imaging (MRI) scans (Hooper, et al, 1982).

THE NET STATE OF IMMUNOSUPPRESSION

It is a truism of transplantation practice that the immunosuppressive therapy administered in order to prevent allograft rejection results in a defect in cell mediated immunity. Thus, the transplant patient is particularly vulnerable to infection with such microbial invaders as the herpes group of viruses, hepatitis, and papovaviruses; such bacterial pathogens as Listeria monocytogenes, Nocardia asteroides, and Mycobacteria species; a variety of fungi ranging from such opportunistic pathogens as Aspergillus species, Mucoraceae, Candida species, and Cryptococcus neoformans, to the geografically restricted mucoses Histoplasma capsulatum and Coccidioides immitis; and such protozoans as Toxoplasma gondii and Strongyloides stercoralis. (Rubin, et al, 1981).

The traditional way of attempting to quantitate the risk of infection with one or more of these agents is to correlate risk with the amount of corticosteroid administered or whether or not such agents as anti-thymocyte globulin have been employed. However, in recent years it has become apparent that such an approach is both too simplistic and unrewarding. A major reason for this is that the whole thrust of modern immunosuppressive therapy is to utilize what might be termed "steroid sparing" therapy. Thus, the interest in cyclosporine, total lymph node irradiation, and polyclonal and monoclonal antibody therapy is based upon the desire to utilize more specific immunosuppressive

therapy that is less globally inhibitory to host defenses than high dose steroid therapy but at the same time prevents allograft rejection (Rubin, et al, 1981).

The most obvious contributors to the net state of immunosuppression are the variety of exogenous immunosuppressive drugs being administered. Other important factors, when present, are neutropenia and, probably, such metabolic factors as uremia and hyperglycemia. The biggest advance, however, in our understanding of the net state of immunosuppression has come with the recognition that certain infections, particularly viruses, are immunosuppressing. For example, in the first 6 months post-transplant, the subgroup of renal transplant patients at highest risk of opportunistic infection is that with changes in circulating T cell subsets (an increase in T suppressor cells and a decrease in T helper cells, "reversed T cell subsets") due to cytomegalovirus and/or Epstein-Barr virus. Similarly, patients with chronic hepatitis and cytomegalovirus infection are at particular risk for Listeria and cryptococcal sepsis. Thus, one of the major factors in determining the risk of life-threatening infection in the transplant patient is the ability of the host defenses to fight such infections, an ability best defined by an assessment of the net state of immunosuppression. This state is determined not only by the exogenous immunosuppressive therapy being administered, but also by certain metabolic factors and the immunomodulating effects of certain viruses that are ubiquitous in this patient population (Rubin, et al, 1981).