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Understanding death before organ donation

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LIST OF ABBREVIATIONS

^{99m}Tc-HMPAO	Technetium-99m hexamthylproply-eneamineoxme
ACTH	Adrenocorticotropic hormone
ADH	Anti-diuretic hormone
AL	Adherent leukocytes
anti-HBc	Antibody against hepatitis B core antigen
antiHBs	Antibodies against hepatitis B surface antigen
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
AtT	Atropine test
AVP	Arginine vasopressin
BAL	Bronchoalveolar lavage
BD	Brain death
BSD	Brain stem death
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBF	Cerebral blood flow
CIT	Cold ischemic time
CMV	Cytomegalovirus
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CPR	Cardio-pulmonary resuscitation
CsA	Cyclosporine
CT	Computed tomography
CTA	Computed tomography angiography
CVP	Central venous pressure
DATPA	Dialysis and Transplant Patient Association
DBD	Donation after brain death
DCD	Donation after cardiac death
DDAVP	L-desamino-8D-arginine vasopressin
DI	Diabetes insipidus

DNA	Deoxyribonucleic acid
DO_2	Oxygen delivery
EEG	Electroencephalogram
ECG	Electro-cardiogram
ERG	Electroretinography
FCD	Functional capillary density
FiO_2	Fraction of inspired oxygen
FT_3	Free triiodothyronine
FT4	Free thyroxine
HBc	Hepatitis B core antigen
HBV	Hepatitis B virus
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
ICAM-l	Intercellular adhesion molecule 1
ICP	Intracranial pressure
ICU	Intensive care unit
IgM	Immunoglobulin M
IL-6	Interlukin 6
IPF	Initial poor function
IR	Ischemic-reperfusion
KFSH&RC	King faisal specialist hospital & research centre
Kim-1	kidney injury molecule-1
LRD	Living related donor
LURDs	Living un-related donors
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MAP-kinases	Mitogen-activated protein kinases
MCP-1	Monocyte chemoattractant protein-1
MEP	Multimodality evoked potentials
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging

NF-κB	Nuclear factor-kappa B
NHBD	Non-heart-beating donor
OLT	Orthotopic liver transplant
OPO	Organ procurement organization
OPTN	Organ procurement and transplantation network
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PBUH	Peace be upon him
PDF	Primary dysfunction
PEEP	Positive end expiratory pressure
PMN	Polymorphonuclear cells
PNF	Primary non-function
PSGL-l	P-selectin glycoprotein ligand-l
PVO_2	Pulmonary vein oxygen level
ROSC	Resumption of spontaneous circulation
rPSGL-Ig	Recombinant P-selectin glycoprotein ligand
rT3	Reverse triiodothyronine levels
SBP	Systolic blood pressure
SCOT	Saudi Center for Organ Transplantation
$ScvO_2$	Central or mixed venous oxygen saturation
SIUT	Sind Institute of Urology and Transplantation
SLC	Sinusoidal lining cells
SPK	Simultaneous pancreas-kidney transplants
SRL	Sirolimus
SVR	Systemic vascular resistance
T3	Triiodothyronine
T4	Thyroxine
TAC	Tacrolimus
TCD	Transcranial dopple
TSH	Thyroid-stimulating hormone
U.K	United Kingdom
UNOS	United network for organ sharing
UW	University of Wisconsin
VCAM-l	Vascular cell adhesion molecule 1

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INTRODUCTION

Introduction

Death is the one great certainty. The subject of powerful social and religious rituals and moving literature, it is contemplated by philosophers, probed by biologists, and combated by physicians. Death, taboo in some cultures, preoccupies others. ***(Morris et al., 1981).***

Dying is a process rather than an event. The determination and certification of death indicate that an irrevocable point in the dying process has been reached, not that the process has ended. Determination of death by any means does not guarantee that all bodily functions and cellular activity, including that of brain cells, have ceased. Several tissues can be retrieved for transplantation long after death has been determined by cessation of circulation. Similarly, after death has been determined by loss of whole brain function, the circulation can be maintained for hours or days to enable organs to be retrieved. Maintaining the circulation can continue even longer: for example, in the case of a pregnant woman, so that the foetus can reach viable independent existence ***(Dobb et al., 2008).***

Understanding death at a biological level was only possible after William Harvey in the 17th century described the circulation of blood and the function of the heart as a pump. Harvey stated that '…the heart is the principle of life…from which heat and life are dispersed to all parts…'. Under this concept, death was when the heart and circulation stopped ***(Harvey, 1628).***

By the end of the 19th century it was known that, during an increase in intracranial pressure **(ICP)**, respirations suddenly stopped whereas the heart continued to beat for some time. It was also recognized that the heart could continue to beat if artificial respiration was performed ***(Cushing, 1902).***

In 1995 Jones stated that, until 30 years ago it was breathing and heartbeat which were taken to signify the continued life of a human being, and it was the permanent cessation of these activities which were taken to constitute human death. However various medical advances throughout the 1950s and 1960s altered the perceived significance of these signs. Recovery from cardiac arrest became more common; mechanical ventilation assisted those not able to breathe spontaneously. Then on December 3rd 1967, the first successful heart transplant was carried out on a human being. The

heart seemed not to be irreplaceable after all. Further, if machines could substitute for the function of the heart or the lungs then these organs could not themselves constitute human life. Only the brain seemed irreplaceable in this way; so criteria for death shifted from referring to heart and lungs to referring to the brain ***(Jones, 1995).***

Physicians, health care workers, members of the clergy, and laypeople throughout the world have accepted fully that a person is dead when his or her brain is dead. In the United States, the principle that death can be diagnosed by neurologic criteria (designated as brain death **(BD)**) is the basis of the Uniform Determination of Death Act ***(Eelco & Wijdicks, 2001).***

Although the law does not define any of the specifics of the clinical diagnosis. There is a clear difference between severe brain damage and BD. The physician must understand this difference, because BD means that life support is useless, and BD is the principal requisite for the donation of organs for transplantation. In adults, the chief causes of BD are traumatic brain injury and subarachnoid hemorrhage. In children, abuse is a more common cause than motor vehicle accidents or asphyxia. ***(Wijdicks, 1995).***

Ulmann, in January 1902, reported the first renal autotransplantation in a dog: grafting a kidney into the neck ***(Ulmann, 1902).***

In 1906, Jaboulay, connected sheep and pig kidneys to the brachial vessels of two patients who were dying of renal failure. Neither kidney worked, but these were the first transplants, albeit xenografts, that had been placed in humans ***(Jaboulay, 1906).***

The techniques used to join the vessels together were those developed and described by Carrel, who is known as the founding father of experimental organ transplantation because of his pioneering work with vascular techniques ***(Carrel, 1902).***

In 1936, the Soviet surgeon Voronoy reported the transplantation of a human kidney to a patient with acute renal failure. There was a major mismatch of blood groups and the kidney never functioned. Voronoy carried out six kidney transplants without success ***(Voronoy, 1937).***

The modern era of clinical transplantation began in the early 1950s, highlighted by the contribution of Kuss et al, Dubost et al, Servelle et al and Michon et al in France, and by Hume et al in Boston. Hume made an early attempt at allografting the kidney from

an unrelated donor and the kidney functioned well, but only for a short period ***(Hume et al., 1955).***

In 1954, Murray and his team carried out the first successful human organ transplant, taking a kidney from an identical twin ***(Merrill et al., 1956).***

This was a landmark event in the history of transplantation. In 1962, Murray performed the first successful cadaveric kidney transplant ***(Merrill et al., 1983).***

In 1963, Starzl achieved the first human liver transplant and Hardy performed the first lung transplant ***(Hardy et al., 1963).***

In 1966, Lillehei et al and Kelly et al carried out the first successful pancreas transplant ***(Kelly et al., 1967).***

The development of immunosuppressive treatment played a crucial role in those early successful organ transplants attempts between unrelated recipients and donors ***(Schwartz, 2000).***

Another milestone event in the history or transplantation occurred in South Africa, on the 3rd December 1967, when Barnard carried out the world's first successful human heart transplant ***(Barnard, 1987).***

In those days, the surgical team brought a brain-dead donor into the operating room with the recipient for the removal; the respirator was then stopped, and everyone waited for the donor's heart to cease to beat. Technically, therefore, those donors were not ''brain dead'' at the time of organ retrieval. Rather, they had been declared dead by classical cardiorespiratory criteria ***(Machado(a), 2005).***

Even when Barnard reported his first successful heart transplant, he stated, ''As soon as the donor had been certified dead (when the electrocardiogram had not shown activity for 5 minutes and there was absence of any spontaneous respiratory movements and absent reflexes) …. The donor chest was then opened rapidly.'' ***(Barnard, 1967).***

DIAGNOSIS OF BRAIN DEATH

Diagnosis of brain death

The clinical neurologic examination remains the standard for the determination of BD and has been adopted by most countries. The clinical examination of patients who are presumed to be brain dead must be performed with precision. The declaration of BD requires not only a series of careful neurologic tests but also the establishment of the cause of coma, the ascertainment of irreversibility, the resolution of any misleading clinical neurologic signs, the recognition of possible confounding factors, the interpretation of the findings on neuroimaging, and the performance of any confirmatory laboratory tests that are deemed necessary. ***(Van Norman, 1999).***

A. Clinical examination:

♦ Preconditions or prerequisites:

1. Coma due to an irreversible acute brain damage* of *known etiology, affecting both hemispheres and brainstem.

It is demanded to have a clear and definite clinical and/or neuroimaging evidence of an acute central nervous system **(CNS)** insult which is consistent with the irreversible loss of neurological function ***(Wijdicks, 2003).***

The loss of function of the brainstem is in a large majority of cases is the infratentorial consequence of extremely severe supratentorial damage, resulting in untreatable ICP. Nevertheless, in some cases, primary brainstem lesions may entirely damage this structure while functioning of the cerebral hemispheres is relatively spared. That can be shown in a number of cases by the presence of some normal activity of the electroencephalogram **(EEG)**. Hence, in primary brainstem lesions we have proposed the use of confirmatory tests ***(Machado, 2007).***

2. Confounding factors should be excluded:

It is essential to exclude the confounding factors that mimic BD ***(Ashwal, 2001).***

a) Un resuscitated shock

It indispensable to apply BD criteria only when MAP is