

Brain Problems in ME/CFS Is There a Simple Explanation?

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THE “TOO MANY SYMPTOMS” SYNDROME

It may be that people with ME/CFS are so commonly and unfairly accused of hypochondriasis because they have too many symptoms to permit credibility. Alternatively, the casual observer may not have had time to listen, does not understand brain function or finds neurological research boring because it seems incomprehensible. This is a tragedy for all concerned. The sick person faces cruel disbelief, the casual observer seems unkind and the research worker lacks recognition for a fascinating and important study which might produce an adequate research grant.

HEART-SINK PATIENTS

ME/CFS is primarily a NEUROLOGICAL illness which may or may not be accompanied by complications affecting skeletal and cardiac muscle, liver, endocrine and lymphoid organs. Whilst most of these can be accepted by the average television viewer as interesting and understandable parts of routine medical and veterinary practice, the problem of belief pertains to the neurological background and its attribution to psychological causes in humans, if not in animals. We therefore have to revise our scanty knowledge of brain function and its variation in disease before making a hasty judgment. Obstacles in the way of improving our knowledge (which is essential for doctors as well as for sufferers) include the fact that the brain is an enclosed organ, sequestered from the rest of the body, devoid of visible movement and not readily accessible for investigation without invasive, expensive or scarce equipment. For centuries philosophers and physicians have debated its functions, the earliest suggestions ranging from the casket of the soul to a device for cooling the blood. Yet, despite four hundred years of technological progress since the invention of the microscope and the current status of molecular biology, biochemistry and brain imaging, we still encounter well educated people prepared to manipulate their observations according to their beliefs. As a result, we have 2 separate camps in modern society - those who do and those who do not “believe” in ME/CFS. Unfortunate sufferers, who have no choice of listeners to their myriad symptoms, gain the inevitable reputation of being “heart-sink patients” - an appellation referring only to the doctor’s sinking heart at the sight of a large medical file and the prospect of too frequent clinic attendances. Recently a group of research psychiatrists active in supporting a psychological origin for ME/CFS has been awarded a generous grant of 190,000 to relieve the NHS of “heart-sink “ problems by the same route [1].

USING OUR EYES - ANATOMICAL INVESTIGATION OF THE BRAIN AND ITS EFFECT UPON “BELIEF”

Apart from organisms which are permanently static and do not require a brain to reorganise purposeful movement, all animated creatures have a brain with the same basic structure. Although its component parts vary greatly in size and proportion in adaptation to the lifestyles of different species, the ground plans invariably include a thick stalk (BRAIN STEM) tapering below to a tap-root like extension (the SPINAL CORD from which a number of paired

SPINAL NERVES emerge) and bearing the above, two hemispherical outgrowths (the cerebrum or CEREBRAL HEMISPHERES) covered by a convoluted sheath of uninsulated nerve fibres (the CEREBRAL CORTEX, an extension of the brain's GREY MATTER). Two similar outgrowths (the little brain or CEREBELLUM) are borne at the base of the brain stem. Although some specific functions can be ascribed to special anatomical sites (eg SPEECH to the CEREBAL CORTEX, lying below the left temple) there are intricate nerve fibre connections to "association areas" such as the PRE-FRONTAL CORTEX, which enable the brain to function as a whole and may permit connected and undamaged nerve cells to restore or take over some function of others, lost because of accident, stroke or infection.

Naked eye examination of the brain at post-mortem, which could reveal scar tissue in Multiple Sclerosis, for example, is unlikely to disclose damage affecting function in ME/CFS, where the changes are more subtle. Investigations require the use of radio-imaging in life (eg. SPECT scans) [2]. or of molecular techniques to amplify viral genetic material (by PCR) [3] at post-mortem. Though deaths from complications such as heart or pancreatic failure, may be officially recorded [4], the lack of attribution to ME/CFS as the underlying disease, encourages insurance companies to "believe" that it is a benign illness and deny pension rights. It is a sad fact that the generosity of many sufferers wishing to donate organs for research is not matched by funding for appropriate scientific investigation.

CAN ANALAGOUS STUDIES OF THE BRAIN IN POLIOMYELITIS LEND CREDIBILITY TO SUFFERERS FROM ME/CFS ?

Using light microscopy and the available histological techniques for studying post mortem material from patients in 1948, BODIAN [5] demonstrated that the main impact of polio virus infection was upon the BRAIN STEM, an area through which almost every important neurological message must pass. A more recent development has been the re-discovery in 1982, of the post-polio syndrome (first recorded in 1875) indicating that survivors of acute polio virus infection, despite apparent stability for some 40 years, may present with new symptoms of incapacitating fatigue, muscle pain and cognitive disturbance, often indistinguishable clinically from ME/CFS. A remarkable series of research papers from 1983 onwards by BRUNO and colleagues [6], using modern investigational techniques in both illnesses, provides strong supportive evidence of similar abnormalities of brain function leading to movement disturbances, anomalies of hormone and neurotransmitter function and of the electrical and chemical activity of the brain (suggesting a central cause for fatigue) as well as of cognitive function. These studies, which link the seemingly bizarre and unconnected symptoms reported by sufferers, should not only revolutionise preconceptions about patients previously considered to be hypochondriacal but encourage them to keep a careful record of all symptoms which can be used as evidence at social benefit tribunals.

HOW DOES THE BRAIN PROCESS INFORMATION?

The brain has often been likened to a computer. However there are fundamental differences in its essential function of processing, comparing and storing information. This is highly developed in humans, making us uniquely creative and better adapted to our environment than any animal. The brain, relies upon specialised cells designed for the reception and transmission of information (nerve cells or NEURONS) which are always electrically active, registering either a low voltage RESTING POTENTIAL or, after rearrangement of positively and negatively charge ions within and without the insulated CELL MEMBRANE, capable of generating a higher voltage ACTION POTENTIAL down its main nerve fibre (AXON). At the

axon tip, chemical transmission (via NEUROTRANSMITTERS, released from the axon) bridges the gap (SYNAPSE) between axon and the receptors (DENDRITES) of the receiving cell. These are spider like outgrowths from the cell body which are simultaneously in contact with axons transmitting from other neurons. Unlike a computer, which can be switched on and off and is programmed to give set answers to a single question, the chemical transmitter bridging the synapse introduces a variability into the on-going message and “NEURONAL PLASTICITY” into the receiving/transmitting network. It has been shown that similar modifications in response may be induced by virus infection [7] and that a change in behaviour may be the only indication of this subtle effect. The brain contains some 100 billion neurons connected to some 10,000 relay stations and this enormous electrical activity creates a massive need for energy, using up 20% of the entire body’s demand for oxygen and glucose. Recent studies of the brain stem by SPECT scan, indicate hypoperfusion and low metabolic activity in subjects with ME/CFS. It is worrying that so many of these patients still smoke and adopt “sugar free” diets, further diminishing supplies of oxygen and glucose.

In order to avoid slowing down the incoming electrical impulses, chemical transmitters must be removed rapidly from the synapse and returned to cell metabolism. However, many drugs are designed to inhibit this process (eg. selective serotonin re-uptake inhibitors such as PROZAC). Despite the manufacturer’s disclaimer and the belief of the patient in chemically manipulated happiness, such drugs can impair the natural production of neurotransmitters and lead to recurrence of the very symptoms for which they have been prescribed [8]. Most ME/CFS patients realise that, in view of their pre-existing brain dysfunction, potentially addictive drugs are better avoided unless used, as advised in the British National Formulary, only for brief periods.

MOVEMENT DISORDERS

The brain is continuously bombarded by incoming signals each of which, after information processing and co-ordination, will initiate an appropriate muscular response (however small). However, there is no single “movement centre” and incoming signals will either be directed via the brain stem to the spinal cord, undergoing processing on the way from specialised centres such as the cerebellum (the brain’s autopilot) or the THALAMUS and BASAL GANGLIA beneath the cerebral hemispheres, all of which act as subsidiary control areas, relieving higher motor centres in the cerebral cortex for more intricate muscular action. Thus, semi automatic movements (eg swimming) co-ordination of movement with visual and sensory input, determination of balance and the mediation of individual limb movements, will pursue a devious pathway, while direct connection is made between the higher motor cortex and muscles requiring exceptionally fine co-ordination such as those of the hand, face and mouth - an arrangement appropriate to the evolutionary tool making, and communication skills of humans. Such muscles are allotted an especially large share of the motor cortex and, when a motor impulse reaches the nerve end plate eg. in finger muscles, it is allocated to a few individual fibres rather than being spread over large areas, as in the leg. Modern research indicates disturbed metabolism in many areas essential to motor control in the brain stem of patients with ME/CFS, the majority of whom have evidence of inco-ordinated muscle twitching after slight exertion. Difficulty with balance and with fine motor control, is often overlooked in medical assessments (especially in children). If patients can be persuaded to send a handwritten letter or children to produce a school notebook, evidence of a marked deterioration in fine motor control compared with previous proficiency or a deterioration in handwriting from one page to the next, can be a valuable aid to diagnosis.

SENSORY DISTURBANCE AND PAIN

The human brain possesses a degree of skill in parallel processing not yet matched by modern computers. Of the five senses (touch, vision, hearing, taste and smell) all pursue devious pathways to various sites in the cerebral cortex for interpretation as well as being linked in parallel processing. Thus, an individual watching television while eating, if examined by SPECT Scan, would demonstrate several areas of the brain simultaneously activated by touch, taste and smell, possibly co-ordinated with vision and hearing. Since vision can only be interpreted in the visual cortex, any damage in the intermediary pathway involving the THALAMUS, for example, will lead to visual disturbance despite a normally functioning eye while distortions of taste and smell may arise from disturbance in the same or adjacent areas of the mid brain through which the signal has passed for interpretation in the SOMATOSENSORY CORTEX. It is not unusual for subjects suffering from ME/CFS to complain of distortions in taste or smell and to ascribe these to allergy while auditory and visual hallucinations may be experienced by individuals where certain neurotransmitters (such as dopamine) are produced in excess. It is important that these patients should record and report seemingly inexplicable symptoms of this type without fear of being disbelieved. Aberrations of touch, pain, pressure and temperature sensation, initially transmitted from skin receptors, are common in ME/CFS and many patients suffer severely from a generalised pain syndrome which may arise from damage to the Thalamus. There is no specific pain centre in the brain but the sensation of pain is normally controlled by natural production of neurotransmitters such as enkephalin which, like synthetic opioids, does not so much remove the pain as render the sufferer indifferent to it. Pain control is difficult in ME/CFS and, if simple measures do not work, it has to be remembered that prolonged use of morphine analogues may reduce natural production of enkephalin. Acupuncture acts to increase local enkephalin production and, together with pleasurable activities which can "gate" pain sensation temporarily, as well as intermittent use of appropriate drugs, these patients may be made more comfortable. However, referral to a specialist pain clinic is often necessary.

HORMONE DISTURBANCE

Hypothalamic function is often disturbed in ME/CFS. The HYPOTHALAMUS is a central relay station for collecting and integrating signals from diverse sources (including the THALAMUS, LIMBIC SYSTEM and RETICULAR ACTIVATING SYSTEM in the brain stem and mid brain) and for producing hormones which affect kidney function and lactation before funneling them into the dependent PITUITARY GLAND, as well as inhibiting or promoting the release of pituitary hormones. In this fashion it has a major influence on specific reaction to stress, thyroid function, weight, appetite and control of glucose metabolism, as well as regulation of female sex hormones and the circadian sleep/temperature rhythm. Most of these hormones are neither difficult nor expensive to measure and there is no case for self medication with thyroid hormones (for example) without accurate laboratory monitoring. Children and adolescents suffer more severely than adults from symptoms of sleep and appetite disturbance as well as from difficulty with emotional control. They should be relieved of school stress as far as possible until their condition stabilises [9]. Unfortunately, because of the hormone dependence of this illness, it is more common and more severe in females in the childbearing years and almost three times as common as in men, who have a more stable hormone profile throughout life.

THE GROWTH OF THE BRAIN, DEVELOPMENT OF MEMORY AND EFFECT UPON EDUCATION

A child's brain, at birth, is no larger than that of Ancient Man and must grow rapidly in the 18 months before the skull bones close to adapt to modern life. Multiplication of neurons, whose axons reach out in random fashion, occurs initially but, unlike a computer, neuronal connections are not irrefutably fixed and can adapt in later life. Neurons which do not achieve connection within the increasingly complex network, die off. In childhood, it is a case of "use it or lose it" and a baby born with a squint will lose visual perception in the "lazy eye" unless nerve connections are made before the age of 5 years. From 11 to 16 years, when the multiplication of new neurons ceases, there is a 5% increase in brain size following which, growth in the complexity of neuronal networks proceeds throughout life. Although young people are quicker to learn, an adult gains in experience and judgement well into healthy old age. These facts underline not only the importance of play and human communication in childhood, but also the devastating effect of educational disadvantage, in the peak learning years of puberty and adolescence, suffered by young people with ME/CFS. At this stage of neuronal growth and increasing complexity of nerve pathways, language function, for example, may never be laid down. Studies of identical twins indicate that experience and memory capacity has a more dramatic effect on neuronal growth and complexity of connections than genetic inheritance.

A good memory demands normal functioning of almost all areas of the cerebral cortex, the basal nerve centres of the mid brain (eg the THALAMUS and HIPPOCAMPUS) and their interconnecting pathways through the brain stem. Fluctuations of the metabolic activity in these areas (often made worse by physical and mental exhaustion) have been reported in SPECT SCANS of patients with ME/CFS [2], the vast majority of whom complain of difficulty with short term memory, though higher intellectual functions are usually preserved.

Normal functioning of the Temporal lobe and other areas of the cerebral cortex is required for:

1. **Short Term Memory**, laid down, for example, by uninterrupted repetition of telephone numbers and lasting for ½ hour. It is not "hard wired" by further processing to link with other memories, and resembles the free floating unassociated thoughts characteristic of dreaming and certain abnormal mental states.
2. **Memory for Simple Facts**, unrelated to time and space.
3. **Implicit Memory**, for automatic sequential repetitive movements appropriate to driving or sports. Sufferers from ME/CFS may experience some of these problems and be well advised to carry shopping lists, limit long distance driving and seek alternative hobbies.

Normal functioning of the entire cerebral cortex is required for:

1. **Memory for Events**, personal and unique to an individual.
2. **Explicit Memory**, which fixes special and personal events in time and space.
3. **Temporary Memory Storage** for 2 years or more in a "scaffolding" of nerve connections in the mid brain.
4. **Long Term Memory Storage**. Memories are retained as increasing experience modifies the nerve connections and, although it is still not quite clear how long term storage is finally accomplished, it depends upon a series of overlapping nerve circuits

involving the entire cerebral cortex. A good memory is the corner stone of the human mind and deprivation of special educational provision in their most formative years is the greatest disability inflicted on young people with ME/CFS [2].

SUMMARY

Patients with ME/CFS cannot be compared with a programmed robot. Damage to vital brain centres (albeit temporary in some cases) may lead to a wide range of apparently unconnected and bizarre symptoms. These are invariably exacerbated by physical exhaustion and mental stress, leading to misinterpretation by the casual observer. Time taken to listen and to examine carefully (aided by a simple scoring chart to assess severity) will do much to prevent patients, who are so often courageous and uncomplaining despite serious disability, from the final indignity of becoming a statistic in "Heart-sink" research.

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