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A CLINICAL AND RADIOLOGICAL INVESTIGATION OF PATIENTS WITH MIGRAINE AND EXTENSIVE WHITE MATTER LESIONS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 1998.

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Medicine, Division of Internal Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination in any other University.



Kapila Ranchhodbhai Hari

1 September 1998

DEDICATION

To Arvind, who is my inspiration.

PUBLICATIONS AND PRESENTATIONS

Hari KR, Modi G, Modi M, Saffer D. Familial Migraine with MRI White Matter Lesions. Neurology Association of S.A. Annual Congress: 1997.

ABSTRACT

Eleven patients with chronic migrainous headaches and extensive white matter lesions as identified on Magnetic Resonance Imaging of the brain were evaluated. The patients ranged in age from 28years to 62years. There were eight females and three males in our group. The patients were all of Southern African descent. None of the patients had a history of migration from a high risk Multiple Sclerosis area. In terms of racial configuration there were five patients of Indian descent, four patients of Mixed Ancestry and two patients who were of Black African origin. There were no White patients in our group. The white matter lesions were identified on Magnetic Resonance Imaging and were found to be localized to the periventricular and subcortical white matter, corpus callosum and the basal ganglia. None of the patients had lesions in the brainstem, cerebellum or spinal cord. Clinically all the patients had a chronic history of migraine and a positive family history for migraine. Each patient had at least one focal neurological event. All the patients suffered from depression. The patients were extensively investigated to exclude demyelination, dysmyelination, vasculitis/vasculopathy and other causes of white matter lesions in the brain. No identifiable cause was elucidated. We concluded that the white matter lesions represent some kind of vasculopathy. We can conclude that these patients have migraine with a vasculopathy which appears to be a distinct subtype of migraine. They may represent a distinct disorder possibly a recessive form or a sporadic occurrence of a CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)-like disorder.

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CHAPTER ONE

PREFACE

AND

INTRODUCTION

The Central Nervous System can be divided into cortical structures, subcortical structures and the spinal cord. Cortical structures are divided into frontal, parietal, temporal and occipital regions. Subcortical structures include the sentrum semiovale, corpus callosum and commissures, basal ganglia including the thalamus, the brainstem (midbrain, pons and medulla) and the cerebellum. In each of these regions we can identify grey matter (cells) and white matter (myelin). One may therefore **artificially** classify diseases that affect the Central Nervous System into those that :

- Affect grey matter only
- Affect white matter only
- Affect grey and white matter

These diseases processes can then be further delineated in terms of cortical, subcortical and spinal cord locations. Pathologically one would consider inherited and acquired diseases in separate categories.

1.1 MIGRAINE

Migraine is a familial, paroxysmal disorder of the Central Nervous System. As with the other paroxysmal disorders, e.g. epilepsy it would be artificially classified as a **grey matter disease.** The disorder has as yet a poorly understood pathogenesis, but recent work by leading authorities in the field have indicated that it is the result of a combination of a disturbance in serotonin metabolism and altered function of the trigeminal vascular system (1). In terms of its clinical profile headache is the dominant symptom. This is usually throbbing in nature and may be unilateral or bilateral. Nausea, vomiting, photophobia and phonophobia are common accompaniments.

The onset of migraine may be in childhood, adolescence or early adult life. The frequency of attacks varies enormously; ranging from one to two times per year to daily attacks.

More importantly the attacks of migraine may be preceded by an **aura** of symptoms akin to the aura in some of the epilepsies. The migrainous aura may constitute motor, sensory or even autonomic symptoms. The aura may occur independently of the headache. The headache on the other hand may occur without an aura. This has led to the arbitrary classification of migraine into **classical** and **common migraine,** the former representing migraine with aura and the latter migraine without aura. Table 1.1 represents a list of the different auras/symptoms that have been described and their relative frequencies.

Table 1.1 (Adapted from:Raskin N.H., Harrisons, Principles of Internal Medicine, Volume 1, Thirteenth edition, McGraw-Hill, Inc. 1994)

Table 1.1

Symptom (aura)	**Percentage affected**
Nausea	87
Photophobia	82
Lightheadedness	72
Scalp tenderness	65
Vomiting	56
Visual disturbances	36
Photopsia	26
Fortification spectra	10
Paresthesias	33
Vertigo	33
Alteration of consciousness	18
Syncope	10
Seizure	04
Confusional state	04

The aura when it occurs remains the same in an individual and with each attack. The constant nature of this in individuals and the specific type has resulted in further delineation of distinct subtypes of migraine. (2,3,4,5)

Opthalmoplegic Migraine

This is defined as migraine associated with paralysis of one or more oculomotor nerves. (6) Transient diplopia may occur with classical migraine but the isolated oculomotor palsies of opthalmoplegic migraine are different in that they may persist for days or weeks after the attack, and sometimes become permanent. The commonest finding is third cranial nerve involvement. The sixth nerve is rarely involved. There may be residual deficits after repeated attacks. A mild mydriasis is the commonest of these with a permanent opthalmoparesis being uncommon. This disorder is more common in children.

Retinal (O ular) Migraine

Unilateral photopsia, monocular altitudinal defects and transient monocular blindness all indicate involvement of the retinal or ciliary circulation. The above symptoms when occurring in isolation with migraine headaches, suggest a diagnosis of retinal migraine. This condition is due to ischaemia of the retinal and anterior optic nerves. The ischaemia can be prolonged and rarely result in a permanent deficit with blindness from optic atrophy and ischaemic papillopathy

Hemiplegic Migraine

This condition is defined as migraine that is regularly associated with episodes of unilateral paralysis. The paralysis may be prolonged and persist for a longer duration than the headache itself. During the event the patient has a hemiparesis or hemiplegia which may or may not be associated with other aura symptoms, such as hemianopic blurring of vision, unilateral paresthesias or numbness, and dysphasia. The symptoms usually last 30 to 60 minutes.

Several families have been described in which this condition was inherited as an autosomal dominant trait (familial hemiplegic migraine). The age of onset of this disease varies from 5 to 30 years, with a predominance during youth. It is thought to be the result of ischaemia in the anterior circulation during, after or preceding an attack of migraine. Minor head trauma and cerebral angiography are well established triggering factors. In the latter disorder, linkage-analysis studies have localized the gene for familial hemiplegic migraine to chromosome 19 (7) and chromosome 1. (8) Hemiplegic migraine has been implicated as a possible aetiology in some of the inexplicable strokes that occur in young women and older adults of both sexes.

Vertebrobasilar Migraine

In this condition, the patients, usually young females with a family history of migraine have symptoms and signs which are consistent with those of ischaemia in the vertebro-basilar territory. The first manifestation is usually visual phenomena. This symptom is unusual in that it occupies both visual fields and may occasionally present

with an episode of cortical blindness. A variety of other symptoms have been described and include vertigo, ataxia, paresthesiae and dysarthria. In children it may be associated with epilepsy or paroxysmal abnormalities in the electroencephalogram. (9) Psychosis, coma and quadriplegia have been documented but are very rare. These symptoms last 10 to 30 minutes and are followed by headache, which is usually occipital. At the time of the headache, patients may have a decreased level of consciousness or even lose consciousness; or become confused. This state may persist for several hours or longer.

It is important to recognize the above syndromes as their recurrence leads to repeated investigations searching for focal lesions.

Genetics of Migraine

The genetics and pathogenesis of migraine are linked. It is widely recognized that migraine is a familial disorder. It does not follow Mendelian genetics (10) and is therefore often described as following a multifactorial pattern of inheritance. The genetic nature of classic migraine is evidenced by its occurrence in several members of the family of the same and successive generations in 60 to 80% of cases (6). The occurrence of hemiplegic migraine as described above appears to provide stronger support to gene disorders in migraine. Hemiplegic migraine is an Autosomal Dominant disorder and it's defect has been identified on chromosome 19p13 in some families. (10) CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) which is also an Autosomal Dominant disorder and has migraine as a major component of the disease has also been localized to chromosome 19p. (11) There is great interest therefore in the link between these disorders and migraine. The current belief is that this kind of abnormal genetics may be the basis of the abnormal chemical and vascular state in migraineurs which is inherited. Thus the disturbances in the trigeminal vascular system and abnormalities of serotonin metabolism are probably transmitted through family members who have the same genetic abnormality.

Pathogenesis of Migraine

To date, it has not been possible to determine from the many clinical observations and investigations, a unifying theory as to the cause and pathogenesis of the common and classic forms of migraine.

Vascular Theory

It has been widely accepted that migraine is due to arterial spasm within the territory of the internal carotid artery. (6) The spasm is thought to be responsible for the aura whilst the dilatation, that occurs in the distribution of the external carotid is believed to account for the headache. Schumacher and Wolff (5) in 1941 showed that the headache is due to arterial dilatation, mainly of the extracerebral arteries of the dura and scalp and branches of the external carotid.

Neuronal Theory

This theory is based on the concept that there is a slow spread of decreased blood flow (oligaemia) over the cortex at a rate of 2-3mm/min. This reduction in blood flow results in reduced neuronal activity, and is based on observations of so-called spreading depression made by Leao (1944), in rat cerebral blood flow. (6) Simplistically this theory proposes that the oligaemia which is thought to begin in the occipital cortex causes the aura. The "rebound" vasodilation that occurs following the oligaemia would result in the headache.

The trigger for the above events is thought to be chemical. Serotonin is believed to be the abnormal chemical in migraine (1,12). Physiologically serotonin constricts large arteries and dilates small arteries and arterioles. In the brain the serotonin neural network is thought to originate in the brainstem raphe nuclei and project upwards into the thalamus and cortex, and downwards into the spinal cord. The role of serotonin in the modulation of pain is well recognized. In migraine it is believed that there may be post-synaptic hyper-reactivity to serotonin release by nerve cells. The receptors inplicated in this hyper-reactivity are those of the trigeminal vascular system. The differential location and different subtypes of serotonin receptors support a selective involvement of the trigeminal vascular system in migraine. The difficulty has been in unifying these three abnormalities viz. neuronal depression, vascular reactivity and chemical imbalance.

Vascular Involvement in Migraine

In terms of vascular involvement in migraine it is yet to be shown that there is any kind of underlying vasculopathy in migraineurs. The occurrence of complicated migraine wherein one of the focal migraine subtypes described above leads to permanent deficit has strongly suggested a significant vascular component to the migraine attack. Patients with hemiplegic migraine can have cerebral infarctions and have residual permanent neurological deficits. There are several reports of this and similar infarctions are noted to occur in all of the subtypes described above (6). These occur in the distribution of an artery and involve grey and/or white matter.

In the condition CADASIL alluded to above (described in detail later) migraine is a dominant component of the disease. (11) Individuals afflicted with this disorder demonstrate clear cerebral infarctions on the basis of an underlying vasculopathy. Strokes, especially within the basal ganglia and subcortical white matter are a key feature of this disease.

The advent of Magnetic Resonance Imaging (referred to as MRI henceforth) and refinement in imaging techniques has resulted in several reports of so-called bright spots in the white matter of migraineurs not having clinical evidence of ischaemia. The frequency of parenchymal abnormalitites associated with migraine ranges from 6% to 40%. (13) These lesions are usually dismissed as non-specific. There have been several studies to determine whether the "spots" represent an underlying vasculopathy. (14,15,16) In a recent retrospective study reviewing 185 consecutive patients who had focal white matter hyperintensities on MRI (16) it was concluded that many of the MRI abnormalities detected in migraine sufferers may be unrelated to migraine especially in the group of patients older than 50years old. In the majority of these patients the white matter lesions (referred to as WML from hereon) represented embolic or vasculitic events resulting from unrelated diseases such as Systemic Lupus Erythematosus, cardiac disease and carotid artery disease. The lesions therefore represent small lacunar-like infarcts in these patients. However, a subgroup of patients exist in whom these WML occur without an underlying or associated cause. These WML are usually dismissed as being of no significance.

In patients with diagnosed migraine, according to the International Headache Society criteria (Appendix 1); I have identified several who have striking neurological symptoms in whom MRI as part of their evaluation revealed central white matter lesions more extensive than those described to date by the authors mentioned above. (13,14, 15,16 and17) In view of this finding the patients were then fully evaluated to determine a cause for the white matter involvement. These findings will be presented in the results section and discussed later. It is at this point therefore essential to my dissertation to discuss and describe in depth the causes of central white matter disease.

1.2 WHITE MATTER LESIONS (WML) OF THE BRAIN

By definition this is a term which is used to refer to a radiological finding. A WML is seen as an increased MRI signal on T2 weighted imaging of the brain. These lesions may vary in size from 1mm to several centimetres. It may resemble a circumscribed circular lesion or widespread breakdown of the white matter, including the corpus callosum. Once identified the lesions indicate a disease process affecting brain white matter. These disease conditions may be classified as inherited or acquired conditions. Disorders of the white matter are due either to dysmyelination or to demyelination. Dysmyelination is defective formation or maintenance of myelin, and demyelination is destruction of myelinated neurons. Dysmyelination starting in early infancy disrupts myelination of most of the neurons in the brain and produces profound neurologic disturbances. The effect is less severe when dysmyelination occurs in older children because more of the brain is already myelinated. At this age, it is often difficult to ascertain whether this or demyelination is responsible for the MRI appearances. Further, demyelination may occur concurrently in some essentially dysmyelination disorders. The precise biochemical and enzymatic defects have been identified in some of the inherited white matter disorders. Diseases in which the cause is unknown are generally categorized as primary white matter disorders. There are many different disorders affecting the white matter, I will focus on the more common and important of these disorders.

1.3 INHERITED DISEASES AFFECTING THE WHITE MATTER

Table 1.2 represents some of the inherited diseases affecting the white matter. (Adapted from:Lee B., Neuroimaging Clinic of North America, White Matter Diseases, WB Saunders Company, May 1993)

TABLE 1.2
1.3.1 Vascular Disorders
1.3.1.1 CADASIL
1.3.1.2 Hemiplegic Migraine
1.3.2 Mitochondrial Disorders
1.3.2.1 Leigh Disease (Subacute necrotizing leukoencephalopathy)
1.3.2.2 MELAS
1.3.2.3MERFF
1.3.3 Perioxisomal Disorders
1.3.3.1 X-linked Adrenoleukodystrophy
1.3.3.2 Neonatal Adrenoleukodystrophy
1.3.3.3 Zellweger's Syndrome
1.3.4 Lysosomal Disorders
1.3.4.1 Lipidosis
1.3.4.2 Mucopolysaccharidoses
1.3.5 Aminoacidopathies / Aminoacidurias
1.3.5.1 Aminoacidopathies
1.3.5.2 Aminoacidurias

1.3.6 Primary White Matter Disorders
1.3.6.1 Alexander's Disease
1.3.6.2 Canavan's Disease
1.3.6.3 Pelizaeus-Merzbacher Disease
1.3.6.4 Cockayne Disease

Disorders of the white matter are due either to dysmyelination or to demyelination. Dysmyelination is defective formation or maintenance of myelin, and demyelination is destruction of myelinated neurons. Dysmyelination starting in early infancy disrupts myelination of most of the neurons in the brain and produces profound neurologic disturbances. The effect is less severe when dysmyelination occurs in older children because more of the brain is already myelinated. At this age, it is often difficult to ascertain whether this or demyelination is responsible for the MRI appearances. Further, demyelination may occur concurrently in some essentially dysmyelination disorders. The precise biochemical and enzymatic defects have been identified in some of the inherited white matter disorders. Diseases in which the cause is unknown are generally categorized as primary white matter disorders.

1.3.1. Vascular Disorders

1.3.1.1 CADASIL (6)

Aetiology

This is an autosomal dominant arteriopathy for which the gene has been mapped to chromosome 19. (18)

Incidence and Age

The true incidence of CADASIL is unknown. It occurs predominantly in young adults although it may present in the fifth to sixth decade. (19)

Pathology

The main features are multiple, small deep cerebral infarcts, a leukoencephalopathy and a nonatherosclerotic nonamyloid angiopathy involving mainly the media of small cerebral arteries. (20) The morphologic hallmark is the presence of a characteristic granular alteration of the arterial media that ultrastructurally corresponds to the accumulation of electron-dense material surrounding the smooth muscle cells. Although the presence of this granular osmiophilic material (GOM) was originally described as limited to brain vessels, identical electron microscopic findings have been demonstrated in the media of peripheral tissue arteries. (21)

Clinical Presentation and Natural History

The disease often starts with attacks of migraine with aura during the third decade. Ischaemic events occur 10 years after the migraine and dementia 20 years after onset of the migraine. Mean duration of the disease is between 20 and 30 years. (11) Death often occurs during the sixth decade. The main clinical presentation is recurrent subcortical events, either transient or more often permanent. The vascular presentation is however not constant and various other symptoms can occur, such as dementia or migraine with aura and depression. These symptoms are usually associated with a history of recurrent strokes but they are occasionally prominent or can be the only manifestation of the disease. Dementia is found in one-third of the overall affected family members and in 90% of subjects before death. (11)

Imaging

Computerized Tomography scans are henceforth referred to as CT scans.

CT: Normal, or there may be multiple confluent white matter lesions concentrated in the basal ganglia and periventricular regions.

MRI: The commonest abnormality is the presence of bilateral confluent ischaemic areas in the basal ganglia and periventricular areas is the most frequently reported finding. The predominant finding is a diffuse, white matter disorder, which is consistent with a widespread small artery disease. The lesions are symmetrical and usually subcortical in distribution. (11)

1.3.1.2 Hemiplegic Migraine

Aetiology

This is an autosomal dominant disorder for which the gene has been mapped to chromosome 19 (6) in some families.

Incidence and Age

The true incidence of Hemiplegic Migraine is unknown. It occurs predominantly in young adults and may responsible for some of the unexplained strokes in young women and older adults of both sexes.

Clinical Presentation and Natural History

The infant, child or adult has episodes of unilateral paralysis that may long outlast the migrainous headache. The mode of onset, lack of seizures, and an apparent relationship to anticardiolipin and antiphospholipid antibodies in some instances imply a vascular pathogenesis. In a variant of this condition there is either unilateral paralysis or aphasia after virtually every minor head injury, but no visual symptoms and the headache is mild. (6) There have also been reports of several infants and young children who have had attacks of hemiplegia (without headache), first on one side then the other, every few weeks. Recovery was complete and investigations including a four vessel angiography in one instance was normal. (6)

Imaging (19)

CT: The scans are usually normal, although cerebral oedema and infarction have occasionally been reported.

MRI: Focal hyperintense lesions in the periventricular white matter on T2 images may be seen, these may correlate with neurologic symptoms in patients with complicated migraine. (22)

1.3.2 Mitochondrial Disorders

The neural damage in this group of disorders is due to defects in the energy-producing systems of many cells and organs.

1.3.2.1 Leigh's Disease

Aetiology

This is a familial or sporadic mitochondrial disorder.

Age

The onset in more than half the cases is in the first year of life, mostly before the sixth month. Patients may present in young adulthood with a variety of clinical features.

Pathology

The main features are bilaterally symmetrical foci of spongy necrosis with myelin degeneration, vascular proliferation and gliosis in the thalami, midbrain, pons, medulla and spinal cord. The basal ganglia are characteristically but not invariably involved. There may be a demyelinative type of peripheral neuropathy.

Clinical Presentation and Natural History

The onset of neurological symptoms is usually subacute or abrupt, sometimes precipitated by a febrile episode or a surgical operation. Infants usually present as floppy babies, and have associated generalized seizures and myoclonic jerks. If the onset is in the second year, there are difficulties in walking, ataxia, dysarthria, intellectual regression, tonic spasms, characteristic respiratory disturbances, external opthalmoplegia, nystagmus and disorders of gaze. (11) In older children dystonia, which may be asymmetrical may predominate. The natural history may be of an acute encephalopathy with very long remissions or of a progressive disease with a variable rate of deterioration.

Imaging

CT: The lesions of the lenticular nuclei and brainstem may be visualized on CT.

MRI: Symmetrical hyperintense foci may be seen in the globus pallidus, putamen and caudate. The periventricular grey matter may similarly be affected. (23)

1.3.2.2 MELAS [Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Symptoms]

Aetiology

This is a familial or sporadic mitochondrial disorder. There is usually a maternal inheritance. 60 to 90% of patients have a mutation at position 3,243 in the tRNA gene of their maternal DNA. (24)

Age

Age of onset of symptoms can range from 3 months to 68 years.

Pathology

The brain and skeletal muscle are the most severely affected organs in these patients (these organs contain nondividing cells). Numerous abnormalities can occur in the brain and include areas of infarction, diffuse myelin and neuronal loss with gliosis, localized areas of oedema with dilated perivascular and pericellular spaces, and areas of calcification in the basal ganglia. Vascular changes in the brain include variation in shape and size of smooth muscle cells with fibrous thickening of intima. Mitochondrial structural abnormalities have also been described in the smooth-muscle cells of vessel walls.

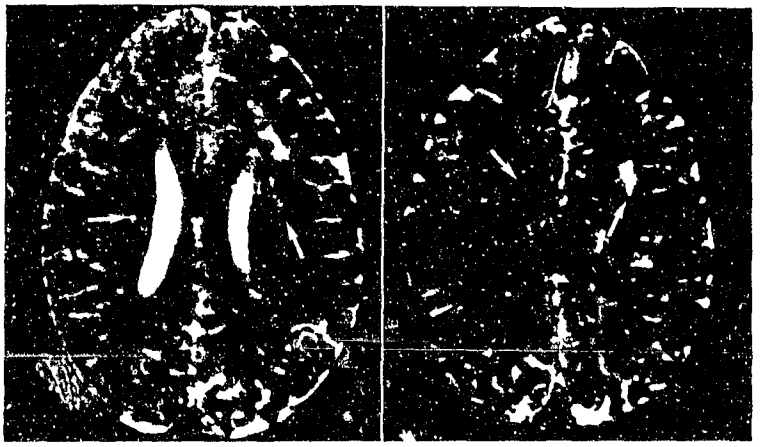
Clinical Presentation and Natural History

In affected patients, normal early development is followed by poor growth, focal or generalized seizures, and recurrent acute episodes that resemble strokes or prolonged transient ischaemic attacks. The stroke deficits often improve but in some patients lead to a progressive encephalopathy. Some patients have hemicranial headaches that cannot be distinguished from migraine. The patients may suffer from repetitive vomiting or episodic lactic acidosis. If there are any characteristic features, they take the form of an unusual clinical pattern of focal seizures, sometimes prolonged, which herald a stroke and have a unique radiographic pattern, involving the cortex and immediate subcortical white matter.

Imaging

CT: There may be numerous low density regions that have no clinical correlates.

MRI: Multiple regions of abnormal signal intensity and enhancement are seen. These regions are representative of infarcts involving the cortex and adjacent white matter. (25)



MELAS. Axial T2-weighted MR scans showing ventriculomegaly and multifocal white matter lesion (arrows) in a 5 year old boy. (22)

1.3.2.3 MERFF [Myoclonic Epilepsy with Ragged Red Fibres]

Aetiology

This is a familial or sporadic mitochondrial disorder. There is usually a maternal inheritance.

Age

Age of onset may vary, although it usually presents in children or young adults. There have however been reports of individuals presenting in the sixth decade of life. (23)

Pathology

The characteristic finding is the presence of ragged red fibres on muscle biopsy.

Clinical Presentation and Natural History

The condition presents with progressive myoclonic epilepsy or myoclonic ataxia. Myoclonus is the most typical feature, and it may be elicited by startle or by movement of the limbs. The nature of the seizure varies but includes drop attacks, focal epilepsy, or tonic-clonic types that are often photo-sensitive. Ataxia tends to worsen progressively, eclipsing the myclonus and seizures in some instances and remaining a minor feature in others. There may be a mild associated myopathy. In addition to the above-mentioned features there may be added features of

mitochondrial diseases that can be present in any mitochondrial disease viz. deafness, mental decline, optic atrophy, opthalmoplegia, cervical lipomas, short stature ... neuropathy.

Imaging

CT: There may be numerous low density regions that have no clinical correlates.

MRI: Multiple regions of abnormal signal intensity and enhancement are present which reflect infarcts involving the cortex and adjacent white matter. (23) (The findings are similar to those in MELAS, discussed above).

1.3.3 Peroxisomal Disorders

Peroxisomes are small intracellular organelles that are involved in the oxidation of very long-chain and monounsaturated fatty acids. Peroxisomal enzymes are also involved in gluconeogenesis, lysine metabolism and glutaric acid metabolism. Peroxisomal disorders are inborn errors of metabolism caused by the deficiency of one or more of these enzymes. X-linked adrenoleukodystrophy is a leukodystrophy caused by a single peroxisomal enzyme deficiency, whereas Zellweger syndrome and neonatal adrenoleukodystrophy affect both the grey and white matter and are caused by multiple enzyme defects.

1.3.3.1 Adrenoleukodystrophy (X-linked)

Aetiology and Inheritance

This is a disorder caused by an impairment in perosisomal oxidation of very long chain fatty acids, leading to their accumulation in the brain and adrenal glands. The deficient membrane protein is encoded by a gene that maps to chromosome X28, close to the gene for colour vision. Inheritance is X-linked recessive.

Pathology

The ventricles are enlarged and there is cerebral atrophy due to white matter volume loss. The cortex is normal. Demyelination classically involves the occipital lobes and

corpus callosum splenium in a bilaterally symmetric pattern. Microscopically the affected cerebral white matter typically has three zones, as follows :

- An innermost central and posterior zone with necrosis, gliosis and sometimes calcification.
- An intermediate zone of active demyelination and inflammatory changes
- A peripheral zone of demyelination without inflammatory reaction

Incidence and Age

X-linked ALD is seen in males. Onset is usually between 4 and 8years of age.

Location

Massive degeneration of the myelin occurs, often asymmetrically in various parts of the cerebrum, brainstem, optic nerves and sometimes spinal cord.

Clinical Presentation and Natural History

The signs of either the adrenal insufficiency or the cerebral lesion may be the first to appear. Visual and behavioural disturbances are the most frequent initial symptoms. Seizures, hearing loss, corticospinal tract involvement and spastic quadraparesis

occur. The interval between the first neurologic symptoms and vegetative state is approximately 2 years.

Imaging

CT : Large, symmetric low density lesions are typically seen in the parieto-occipital regions. Enhancement may be seen in the advancing rim, surrounded by a more peripheral non-enhancing oedematous zone.

MRI : The three histopathologic zones described in ALD can be delineated on MR. The central necrotic zone is seen as a low signal region on T1 weighted images. The intermediate zone of active demyelination and inflammation enhances follows contrast administration.

1.3.3.2 Neonatal Adrenoleukodystrophy

Aetiology and Inheritance

This is an autosomal recessive disorder involving multiple enzymes.

Pathology

The ventricles are enlarged and there is cerebral atrophy due to white matter volume loss. The cortex is normal. Microscopically the affected cerebral white matter typically has three zones, as follows:

- An innermost central and posterior zone with necrosis and gliosis. Calcification is occasionally present.
- An intermediate zone of active demyelination and inflammatory changes
- A peripheral zone of demyelination without inflammatory reaction

Incidence and Age

This form represents 40% of all adrenoleukodystrophy cases. (26)

Clinical Presentation and Natural History

Neurologic abnormalities precede adrenal insufficiency in over 80% of cases. (26)

Imaging

CT : Large, symmetric low density lesions are typically seen in the parieto-occipital regions. Enhancement may be seen in the advancing rim, surrounded by a more peripheral non-enhancing oedematous zone.

MRI : The abnormalities described above for ALD are present. The abnormalities are however distributed throughout the white matter with no predilection for the occipital lobes. (25)

1.3.3.3 Zellweger's Syndrome

Aetiology and Inheritance

This is an autosomal recessive neurodegenerative disorder involving multiple enzymes.

Pathology

In the brain there is an unusual combination of abnormalities; neuronal migrational disorders with heterotopic grey matter, pachygyria and polymicrogyria can occur.

Age

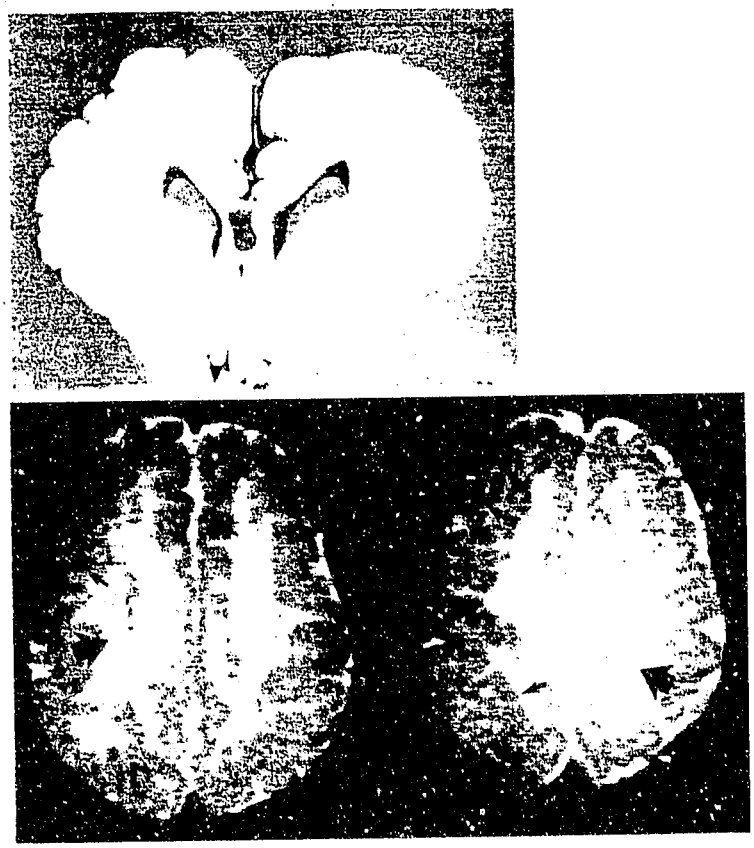
It presents in infancy.

Clinical Presentation and Natural History

Affected individuals have characteristic facial features and progressive psychomotor retardation.

Imaging

MRI : T2 images show pachygyria, periventricular heterotopias, cerebral white matter hypomyelination and cortical neuronal loss. (26)



Zellweger's Syndrome. Coronal gross autopsy specimen showing hypomyelination with scanty white matter. The cortex is thickened and has foci of polymicrogyria. Axial T2-weighted MR scans demonstrate hypomyelination, markedly decreased white matter volume (large arrows) and polymicrogyria (small arrows). (22)

1.3.4 Lysosomal Disorders

1.3.4.1 Lipidosis

This is the generic term for accumulation of various phospholipids and glycolipids. The complex metabolism involves degradation of: cerebroside, ganglioside, sulfatide and sphingomyelin into fatty acid and sphingosine. Deficiency of the appropriate enzymes results in accumulation of these substances systematically or in the brain.

1.3.4.1.1 Krabbe Disease (Globoid Cell Leukodystrophy, GLD)

Aetiology and Inheritance

This is a lysosomal disorder caused by a deficiency of the lysosomal hydrolase galactocerebroside beta-galactosidase. Inheritance is autosomal recessive.

Pathology

The brain is small and atrophic. Extensive symmetric dysmyelination of the centrum semiovale and corona radiata with subcortical arcutate fibre sparing is seen. The cerebellar white matter is affected to a lesser degree. Microscopically there is myelin loss with astrogliosis. Perivascular clusters of large multinucleated "globoid" and mononuclear epitheliod cells are present in the demyelinated zones.

Incidence and Age

There is a reported incidence of 1: 50000 in Sweden but it is much lower elsewhere. (26) Three different types of this disease are recognised according to the age at onset. These are the infantile, late infantile, and adult forms.

Location

The centrum semiovale and periventricular white matter are most severely affected. The subcortical U fibres are relatively spared.

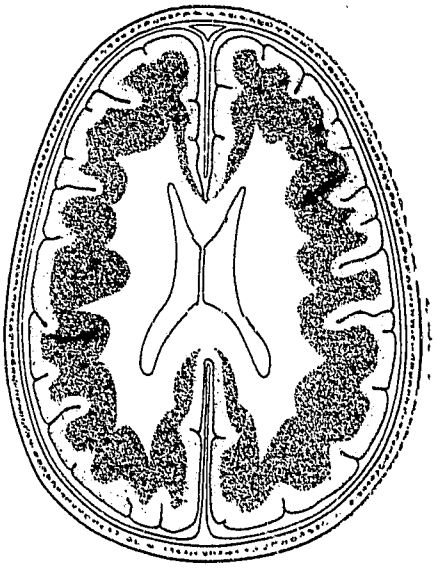
Clinical Presentation and Natural History

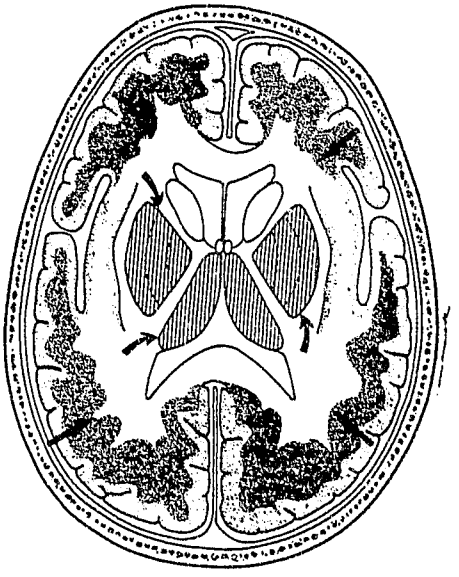
Psychomotor deterioration, irritability, optic atrophy, and cortical blindness are seen. Seizures may occur in the later stages of the disease. Krabbe disease typically is rapidly progressive and fatal.

Imaging

CT : The thalami and basal ganglia often appear hyperdense. The corona radiata and cerebellum may show similar changes. Diffuse low densities are present in the periventricular white matter. No enhancement occurs following contrast administration.

MRI : Nonspecific confluent, symmetric periventricular white matter hyperintensities are present on T2-weighted images. Late-onset disease may show changes limited to the posterior hemispheric white matter. Severe progressive atrophy occurs in the infantile form of GLD.







Krabbe Disease. Anatomic diagrams demonstrate periventricular white matter demyelination. Axial T2-weighted MR scan in a 10 month old child with Krabbe. The periventricular demyelination (arrows) is typical but not pathognomonic for Krabbe. (22)

1.3.4.1.2 Metachromatic Leukodystrophy (MLD)

Aetiology and Inheritance

This is a lysosomal disorder caused by a deficiency of the catabolic enzyme arylsulfatase A. Inheritance is autosomal recessive.

Pathology

Symmetrical demyelination occurs. The subcortical U fibres are usually spared. The cerebellum is often atrophic. Microscopic findings include axonal loss with astrogliosis. A metachromatic lipid material, galactosylceramide sulfatide, accumulates in the peripheral and central nervous system white matter.

Incidence and Age

This is the most common hereditary leukodystrophy, with a prevalence of 1 in 100,000 newborns. (26) Three different types of this disease are recognised according to the age at onset. These are the late infantile, juvenile and adult forms. Approximately 80% of cases occur in childhood with onset typically between 1 and 2 years of age. (26)

Location

The deep periventricular white matter is involved with the arcuate fibres typically spared until late in the disease process. The anterior white matter is more severely affected.

Clinical Presentation and Natural History

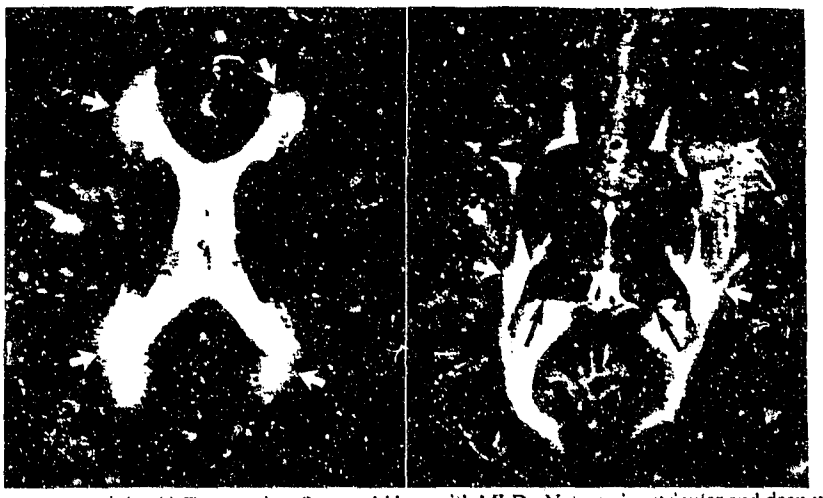
In the most common form, late infantile MLD, motor signs of peripheral neuropathy are followed by deterioration in intellect, speech and co-ordination. Within 2 years of onset, gait disorders, quadriplegia, blindness and decerebrate posturing can be seen. The disease process is rapidly progressive and death occurs within 6 months to 4 years following symptom onset.

Imaging

CT : There is moderate ventricular enlargement. Low density lesions are present, progressing anteriorly to posteriorly within the white matter. There is no enhancement following contrast administration.

MRI : Diffuse confluent high signal is present in the periventricular white matter on T2 weighted images. Initially the arcuate fibres are spared. A striking feature in many cases is increased signal in the cerebellar white matter. The thalami may appear mildly to extremely hypointense. Cortical and subcortical atrophy often occurs in later

stages of the disease, particularly when myelin loss extends into the subcortical arcuate fibres.



Axial T2weighted MR scans in a 9 year old boy with MLD. Note periventricular and deep white matter high signal areas (white arrows). The thalami are abnormally hypointense (black arrows). (22)

1.3.4.1.3 Fabry's Disease)

Aetiology and Inheritance

The primary deficit is in the enzyme alpha-galactosidase A. This condition is inherited as a X-linked recessive trait.

Pathology

The primary deficit is in the enzyme alpha-galactosidase A, the result of which is the accumulation of ceramide trihexoside in endothelial, perithelial and smooth muscle cells of the blood vessels and in nerve cells in many parts of the nervous system (hypothalamic and amygdaloid nuclei, substantia nigra, reticular and other nuclei of the brainstem, anterior and intermediolateral horns of the spinal cord, sympathetic and dorsal root ganglia).

Age

The disease becomes clinically evident in childhood or adolescence

Clinical Presentation and Natural History

The patients initially present with intermittent lancinating pains and dysesthesias of the extremities. The dysesthesias may be evoked by fever, hot weather and vigorous exercise. Usually there is no sensory loss but autonomic features have been recorded.

Thrombotic infarctions occur in the brain during early adult years. Diagnosis is usually made by the presence of characteristic cutaneous and corneal lesions.

Imaging

MRI : Neurologic lesions that are thought to be the result of thromboses of small cerebral vessels may be seen. Increased T2 signal in the basal ganglia may indicate infarcts. Hyperintensities may be visualized in the white matter on T2 imaging.

1.3.4.1.4 Tay-Sachs Disease

Aetiology and Inheritance

The basic enzymatic abnormality is a deficiency of hexosaminidase A_s which normally cleaves the N-acetyl-galactosamine from gangliosides. Inheritance is autosomal recessive.

Pathology

The brain is large, sometimes twice the normal weight. In addition, there is loss of neurons and a reactive gliosis. The remaining nerve cells throughout the CNS are distended with glycolipid.

Incidence and Age

It occurs mostly in Jewish infants of eastern European background. The disease becomes apparent in the first weeks and months of life, almost always by the fourth month.

Clinical Presentation and Natural History

The first manifestations are an abnormal startle response to acoustic stimuli, listlessness, irritability and poor reactions to visual stimuli. These features are followed by a delay in psychomotor development or regression with inability to roll over and sit. Initially axial hypotonia is prominent, but later there are spasticity and other corticospinal tract signs and visual failure. Cherry-red spots with optic atrophy are observed in the retinas in more than 90% of patients. (6) In the second year, there are tonic-clonic or minor motor seizures and an increasing size of the head with relatively normal ventricles. In the third year dementia, decerebration, blindness and cachexia are seen.

Imaging

MRI : Non-specific increased white matter signals have been described (25)

1.3.4.1.5 Niemann-Pick Disease

Aetiology and Inheritance

The basic enzymatic abnormality is a deficiency of the enzyme sphingomyelinase. Inheritance is autosomal recessive.

Pathology

Neurons are decreased in number, and many of the remaining ones are pale, ballooned and granular. The most prominent neuronal changes are seen in the midbrain, spinal cord and cerebellum. The white matter is little affected. Foamy histiocytes (Niemann-Pick cells) that fill the viscera contain sphingomyelin and cholesterol; the distended nerve cells contain mainly sphingomyelin.

Incidence and Age

Two-third of the affected infants have been of Ashkenazi Jewish parentage (20). The onset of symptoms is between 3 and 9 months of age. (23)

Clinical Presentation and Natural History

The initial manifestations are frequently enlargement of the liver, spleen and lymph nodes. Neurological involvement is definite by the end of the first year, often earlier; the usual manifestations are loss of spontaneous movements, lack of interest in the

environment, axial hypotonia with bilateral corticospinal signs, blindness and amaurotic nystagmus, and a macular cherry-red spot. Most patients succumb to an intercurrent infection by the end of the second year.

Imaging

MRI : Non-specific increased white matter signals have been described, although the midbrain, spinal cord and cerebellum are the regions most affected (25).

1.3.4.1.6 Gaucher's Disease

Aetiology and Inheritance

The basic enzymatic abnormality is a deficiency of the enzyme glucocerebroside. Inheritance is autosomal recessive.

Pathology

Glucocerebroside accumulates in the involved tissues. The characteristic pathologic feature is the Gaucher cell – a wrinkled appearance of the cytoplasm and eccentricity of the nucleus. In the brain, the main abnormality is a loss of nerve cells, particularly in the bulbar nuclei and a reactive gliosis.

Age

The onset of the neuronopathic form is usually before 6 months and frequently before 3 months.

Clinical Presentation and Natural History

The affected infants have rapid loss of head control, ability to roll over and of purposeful movements. Most patients do not survive beyond 2 years.

Imaging

MRI : Non-specific increased white matter signals have been described.

1.3.4.2 Mucopolysaccharidoses

1.3.4.2.1 Type I Hurler's

1.3.4.2.1 Type II Hunters

1.3.4.2.3 Type III San Filippo

1.3.4.2.4 Type IV Morquiol.

1.3.4.2.5 Type VI Maroteaux-Larny

1.3.4.2.6 Type VII Sly

(N.B. Type V is no longer used as part of the classification.)

In this group of diseases lipid is stored in neurons and polysaccharides are stored in connective tissues. There exists therefore a combination of neurological and skeletal abnormalities. Six distinct clinical subtypes are recognized (Type V is no longer used). The basic abnormality is an enzymatic defect that prevents the degradation of glucosaminoglycans. These diseases are all autosomal recessive except the Hunter syndrome which is sex-linked. Each type of mucopolysaccharidosis is caused by a defect in a different enzyme.

MRI : The appearances range from subtle loss of grey and white matter distinction to markedly increased T2 signal associated with extreme dilatation of the ventricles. The increased signal throughout the white matter in addition to the periventricular hyperintensity, may represent poor myelination. **Multiple lacunar defects throughout the white matter** are visible on T1. These have been shown to be due to enlarged perivascular spaces associated with focal demyelination. (25)



Hurler's Disease. A T1-weighted imahe shows multiple cavities in the white matter. T2-weighted image shows the region's increased signals are larger than those shown on T1-weighted image. (14)

1.3.5. Aminoacidopathies and Acidurias

These autosomal recessive enzymatic defects involve the pathways of amino acid metabolism. Amino acids are responsible for the formation of proteolipids, which are essential components of myelin. Defects in amino acid metabolism therefore result in failure of myelination (dysmyelination) but may also be responsible for breakdown of formed myelin (demyelination). The exact mechanism of these processes is unclear. Deficiency of a specific enzyme (aminoacidopathy) results in systemic accumulation of the affected amino acid (aminoacidaemia), which is secreted in excessive quantities in the urine (aminoaciduria). Rarely defects in the transport mechanisms result in failure to reabsorb amino acid in the renal tubules (aminoaciduria without aminoacidaemia).

1.3.5.1 Aminoacidopathies

1.3.5.1.1 Phenylketonuria (PKU)

Aetiology and Inheritance

This is an aminoacidopathy caused by defective hepatic phenylalanine hydroxylase, an enzyme required for the conversion of phenylalanine to tyrosine. Inheritance is autosomal recessive.

Incidence and Age

The incidence is 1 in 14000. (26) Patients with this disorder are normal at birth, but if untreated develop mental retardation associated with other neurological abnormalities.

Location

The deep periventricular white matter is involved. The subcortical U fibres are usually spared.

Clinical Presentation and Natural History

In the classic form of PKU the impairment of psychomotor development can usually be recognised in the latter part of the first year. Hyperactivity, aggressivity, clumsy posturings, repetitious digital mannerisms, and slight corticospinal tract signs are the usual clinical manifestations.

Imaging

CT: Periventricular hypodensities may be seen.

MRI: Varying degrees of demyelination occur, usually involving the periventricular white matter. Increased signal in the periventricular deep cerebral white matter can be identified on T2 weighted scans. This is not specifically diagnostic of PKU. MRI is a valuable tool in assessing the efficacy of dietary treatment and patient compliance.

1.3.5.1.2 Tyrosinaemia

Aetiology and Inheritance

This disease is caused by defective action of tyrosine carboxylase. Inheritance is autosomal recessive.

Age

The disease typically presents toward the end of the first or second year.

Clinical Presentation and Natural History

Mild to moderate mental retardation is common. There may be self-mutilation and inco-ordination of limb movements. A low-tyrosine diet has resulted in improvement of symptoms but must be started early.

Imaging

MRI: Varying degrees of demyelination occur, usually involving the periventricular white matter.

1.3.5.1.3 Maple Syrup Urine Disease

Aetiology and Inheritance

This disease is caused by failure to catabolize branched-chain amino acids (leucine, isoleucine and valine). Inheritance is autosomal recessive.

Age

The disease typically presents within 4 to 7 days after birth.

Clinical Presentation and Natural History

The affected infants have a severe, rapidly progressive neurologic deterioration. Death occurs within one year if the disease is left untreated.

Imaging

MRI: Initially a marked, generalized diffuse oedema appears and remains for 6 to 7 weeks in untreated infants. The oedema then decreases and is transformed into better demarcated periventricular white matter disease. A characteristic, more intense local oedema involves the deep cerebellar white matter, dorsal brainstem, cerebral peduncles and posterior limbs of the internal capsule. (25)

1.3.5.1.4 Homocystinuria

Aetiology and Inheritance

It is due to an inborn error of metabolism of methionine. Inheritance is autosomal recessive.

Clinical Presentation and Natural History

The patients are tall, slender and have long limbs. They may have scoliosis. Arachnodactyly, thin and weak muscles, highly arched feet and kyphosis are the typical skeletal features that occur in this condition. A dislocation of one or both lenses (usually downward) may occur. The only neurologic abnormality is mild mental retardation. An abnormality of platelets favouring clot formation and thrombosis of cerebral arteries has been suggested. Clinical manifestations consist of multiple cerebrovascular lesions, dementia, epilepsy and polyneuropathy.

Imaging

MRI: Multiple small arterial thromboembolic infarcts, sagittal sinus thrombosis and deep cerebral venous occlusions with infarctions may occur. These infarctions may present as hyperintensities in the white matter on T2 imaging.

1.3.5.1.5 Methylmalonic Acidaemia

Aetiology and Inheritance

There is a block in the conversion of methylmalonyl-CoA to succinyl-CoA. Inheritance is autosomal recessive.

Clinical Presentation and Natural History

Clinically there are progressive neurologic defects which are characterized by extrapyramidal features.

Imaging

CT: There may be bilateral low density lesions in the globus pallidus.

MRI : Decreased signal intensity is seen in the regions corresponding to the CT lesions. There may also be symmetric hyperintensities seen in the white matter on T2 images.

1.3.5.1.6 Glutaric acidaemia Type 1

Aetiology and Inheritance

This is caused by defective glutyl coenzyme A dehydrogenase, which is responsible for the breakdown of lysine to tryptophan. Inheritance is autosomal recessive.

Clinical Presentation and Natural History

Clinically there are progressive neurologic defects which are characterized by extrapyramidal features.

Imaging

CT: The putamen and caudate nuclei show bilateral low density lesions.

MRI : Decreased signal intensity is observed in the areas which correspond to the CT abnormalities. Symmetrical hyperintensities are seen in the white matter on T2 images.

1.3.5.2 Aminoacidurias

1.3.5.2.1 Oculocerebrorenal (Lowe's) Syndrome

Aetiology and Inheritance

This condition is a due to a defect in amino acid transport. The mode of inheritance is probably X-linked recessive although sporadic cases have been reported in females.

Age

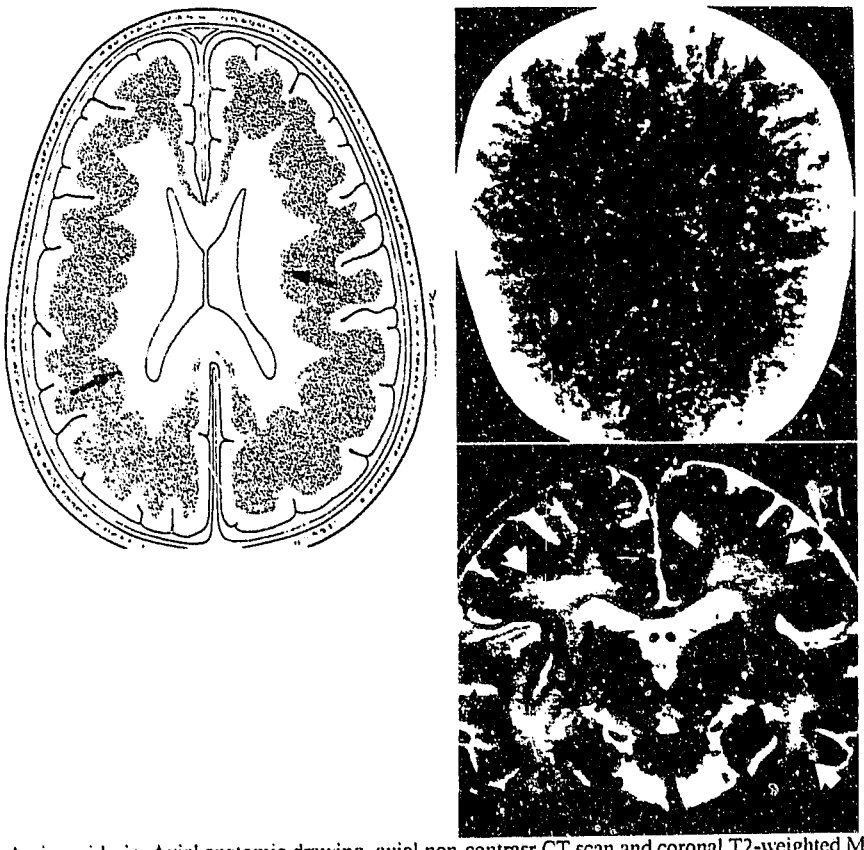
The onset is in infancy.

Clinical Presentation and Natural History

The clinical abnormalities include bilateral cataracts (which may be present at birth), glaucoma, corneal opacities and blindness, pendular nystagmus, hypotonia and depressed reflexes, corticospinal signs without paralysis, occasional seizures and psychomotor retardation.

Imaging

MRI: Non-specific patchy increased T2 signal has been reported in the white matter. Multiple lacunar defects may be associated with these white matter changes.



Aminoaciduria. Axial anatomic drawing, axial non-contrasr CT scan and coronal T2-weighted MR scan depict the extensive but nonspecific periventricular demyelination seen in most aminoacidurias. (22)

1.3.6.Primary White Matter Diseases

1.3.6.1 Alexander's Disease

Aetiology and Inheritance

Sporadic leukoencephalopathy of unknown aetiology. A familial incidence has not been reported.

Age

The onset is in infancy.

Clinical Presentation and Natural History

The affected infant has a failure to thrive, psychomotor retardation and seizures. An early and progressive macrocephaly has been a consistent feature.

Imaging

MRI: Characteristic frontal lobe hyperintensities are seen on T2 images. These lesions may occur in the white matter.

1.3.6.2 Canavan's Disease

Aetiology and Inheritance

There is a deficiency of aspartoacylase. Inheritance is autosomal recessive.

Age

Onset is early, often recognizable in the first three months of life.

Clinical Presentation and Natural History

There is either a lack of development or rapid regression of psychomotor function, loss of sight and optic atrophy, lethargy, difficulty in sucking, irritability, reduced motor activity, hypotonia followed by spasticity of the limbs with corticospinal signs and an enlarged head.

Imaging

CT: There is confluent attenuation of cerebral of cerebral and cerebellar white matter in an enlarged brain with relatively normal ventricles.

MRI : Diffuse high signal intensities are seen on T2 images. These lesions may occur in the white matter.

1.3.6.3 Pelizaeus-Merzbacher Disease

Aetiology and Inheritance

There is a defective synthesis of proteolipid protein, one of the two myelin basic proteins. Inheritance is X-linked.

Age

Onset is early, often recognizable in the first months of life, although it may begin later in childhood.

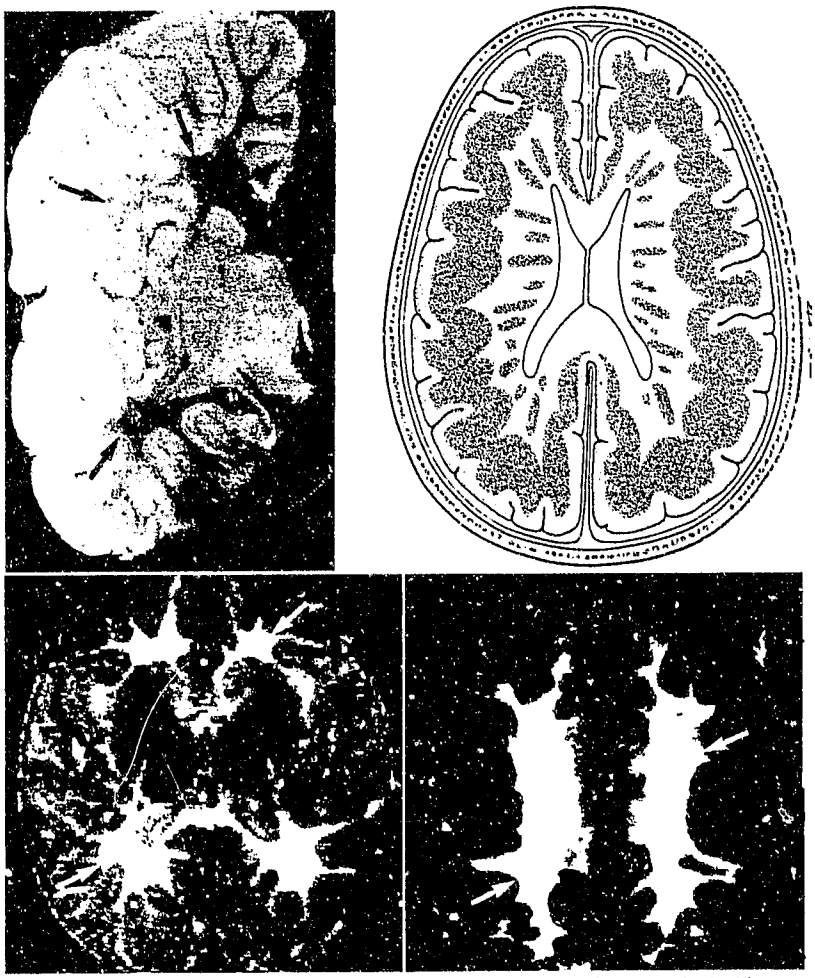
Clinical Presentation and Natural History

The first signs are abnormal movements of the eyes. There is spastic weakness of the limbs, ataxia, optic atrophy, intention tremor, choreiform or athetotic movements of the arms and slow psychomotor development. In later developing cases cerebellar ataxia and mental retardation are prominent features.

Imaging

CT: Mild, non-specific cerebellar and cerebral atrophy may be seen. The white matter may appear normal or show diffuse low intensity changes.

MRI : There are widespread white matter abnormalities. In severe cases there is near-total lack of normal myelination. (25)



Pelizaeus-Merzbacher disease. Coronal gross pathology specimen shows marked white matter hypomyelination. Axial anatomic drawing shows extensive periventricular demyelination. Axial T2-weighted MR scans in a 8 year old boy displays extensive high intensity signal throughout the white matter (22).

1.3.6.4 Cockayne Disease

Aetiology and Inheritance

No specific biochemical abnormality is found. Inheritance is autosomal recessive in some families.

Age

Onset is in late infancy.

Clinical Presentation and Natural History

The main clinical findings are stunting of growth, evident by the second and third years; microcephaly; retinitis pigmentosa; cataracts and blindness; delayed psychomotor and speech development; spastic weakness and ataxia of limbs and gait. There may occasionally be athetosis and amyotrophy with abolished reflexes.

Imaging

MRI : Widespread white matter abnormality is evident. Severe cases show near-total lack of normal myelination (as for Pelizaeus-Merzbacher Disease).

1.4 ACQUIRED DISEASES AFFECTING THE WHITE MATTER

Numerous acquired disease process may affect primarily or exclusively the cerebral white matter (see Table 1.3). Specific age-related changes take place in the cerebral white matter and are also considered below for completeness sake.

Table 1.3 represents some of the acquired diseases affecting the white matter. (Adapted from:Lee B., Neuroimaging Clinic of North America, White Matter Diseases, WB Saunders Company, May 1993)

TABLE 1.3
1.4.1 Demyelinating Disorders
1.4.1.1 Multiple Sclerosis
1.4.1.2 DEVIC,s Syndrome
1.4.2 Vascular Disorders
1.4.2.1 Age related
1.4.2.2 Hypoxic Ischaemic Encephalopathy
1.4.2.3 Subcortical Arteriosclerotic Encephalopathy
1.4.2.4 Vasculitis
1.4.2.4.1 Primary CNS angiitis
1.4.2.4.2 Secondary CNS Vasculitis
1.4.2.5 Hypertensive Encephalopathy
1.4.2.6 Cerebral Amyoid Angiopathy

1.4.2.7 Eclampsia
1.4.2.8 Antiphospholipid Antibody Syndrome
1.4.2.9 Migraine
1.4.3 AIDS-related White Matter Diseases
1.4.3.1 AIDS Dementia Complex
1.4.3.2 Progressive Multifocal Leukoencephalopathy
1.4.3.3 Cytomegalovirus Infection
1.4.3.4 Varicella-Zoster Virus Infection
1.4.3.5 Primary CNS Lymphoma
1.4.4 Viral and Post-Viral Demyelination
1.4.4.1 Infectious Demyelination
1.4.4.2 Subacute Sclerosing Panencephalitis
1.4.4.3 Post-Viral Demyelination
1.4.4.4 Acute Disseminated Encephalomyelitis
1.4.5 Toxic Demyelination
1.4.5.1 Chronic Alcoholism
1.4.5.2 Wernicke's Encephalopathy
1.4.5.3 Marchiafava-Bignami Disease
1.4.5.4 Osmotic Demyelination
1.4.5.5 Hydrocarbons and other solvents
1.4.6 Iatrogenic
1.4.6.1 Chemotherapy
1.4.6.2 Radiation
1.4.7 Trauma

1.4.1.1 Multiple Sclerosis [MS]

Aetiology and Inheritance

The precise aetiology of this disease is unknown, although most investigators favour autoimmune-mediated demyelination in genetically susceptible individuals. (27, 28) The incidence varies considerably and is influenced by race, geographical region, familial tendency and genetic factors amongst other factors.

Pathology

Gross pathology: Plaques are visible. Typically it consists of an oedematous pinkish white matter lesion. Chronic lesions commonly consist of necrosis with atrophy and cystic changes.

Microscopic pathology: Myelin and myelin-producing oligodendrocytes are destroyed. The lesions can be histologically defined as active or inactive depending on the presence or absence of perivascular inflammation.

Incidence and Age

This is the most common demyelinating disease except for age-related vascular disease. It mainly affects young adults of North European extraction and occurs most often in temperate climates, but has world-wide racial and geographic distribution.

Symptom onset is usually between 20 and 40 years of age. The incidence in females is higher.

Clinical Presentation and Natural History

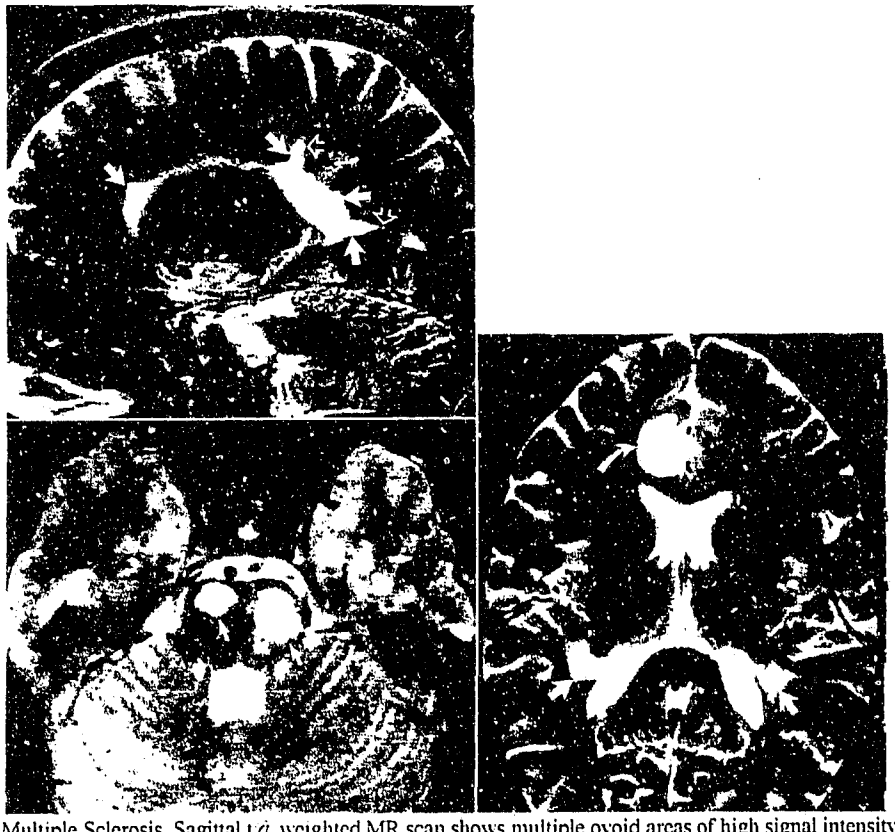
MS is characterized clinically by episodes of focal disorder of the optic nerves, spinal cord and brainstem which remit to a varying extent and recur over a period of many years. The clinical manifestations are varied and are determined by the location and extent of the demyelinative foci. The lesions have a predilection for certain portions of the Central Nervous System resulting in complexes of signs and symptoms that can often be regarded as characteristic of MS.

Imaging

In a prospective 2-year study, the sensitivity of MR imaging in detecting MS was nearly 84%. (29) It exceeded all other tests, including oligoclonal bands, evoked potentials and CT scans. Imaging findings vary with disease activity, although clinical correlation with specific lesions is generally poor. Most foci identified on standard MR scans are clinically silent.

CT : These are often normal early in the disease course. Lesions are typically iso- or hypodense with brain on non-contrast scans. Enhancement following contrast administration is variable. Some lesions show no change, whereas others enhance intensely. Both solid and ringlike patterns are observed. Some lesions only become apparent after high-dose delayed scans are performed.

MRI (29): Most MS plaques are iso- to hypointense on T1 weighted scans and hyperintense compared to brain on T2 weighted scans. There are many causes of white matter hyperintensities on T2 images therefore most authorities require the presence of three or more discrete lesions that are 5mm or greater in size, as well as lesions that occur in a characteristic location and have a compatible clinical history, to establish the MR diagnosis of MS. Oblong lesions at the calloso-septal interface are typical. Periventricular extensions into the deep white matter, the so-called **Dawson's fingers**, are characteristic of the condition. MS lesions are often seen as round or ovoid areas with a beveled appearance on T1 and proton density weighted images. Confluent periventricular lesions are common in severe cases. Abnormal basal ganglia hypointensities are seen in about 10% of long-standing severe MS cases. Enhancement following contrast administration represents blood-brain barrier disruption. Enhancement is highly variable and typically transient, seen during the active demyelinating stage. Both solid and ringlike enhancement patterns can be seen. Enhanced T1 weighted scans can detect additional lesions that are not apparent on T2 images, although most MS plaques do not enhance following contrast administration. Some solitary or highly atypical MS lesions may be indistinguishable from abscesses or neoplasms. Cranial neuropathies, particularly optic neuritis, are common in patients with MS. Lesions in the brainstem tracts and nuclei are seen on T2 images whereas contrast-enhanced T1 images may delineate enhancement in the nerves themselves.



Multiple Sclerosis. Sagittal t$\hat{a}$ weighted MR scan shows multiple ovoid areas of high signal intensity along the callososeptal interface (large arrows). Note the periventricular extension into the sentrum semiovale (Dawson's fingers). Axial T2-weighted Mr scans show multiple brainstem lesions ina 16 year old girl. Axial T2-weighted MR scans shows typical periventricular plaques and a large frontal plaque that involves the cortex. (25)

1.4.2 Vascular Disorders

1.4.2.1 Aging

There are certain imaging findings that mirror normal alterations in the aging brain. Specific age-related changes take place in the cerebral white and grey matter, the cerebrospinal fluid spaces, and the basal ganglia.

Foci of increased signal intensity are often identified on T2 weighted MR scans in demented and healthy elderly patients. The clinical significance of these findings is uncertain, and their precise aetiology remains unclear. These foci are found in several different locations :

1.4.2.1.1 Virchow-Robin Spaces (VRS)

These are normal perivascular spaces. These are pial-lined extensions of the subarachnoid space that surround penetrating arteries as they enter either the basal ganglia or the cortical grey matter over the high convexities. They may extend deep into the basal ganglia and centrum semiovale. Small VRS are found in patients of all ages and are a normal anatomical variant. VRS increase in size and frequency with advancing age. VRS are less frequently identified in the high-convexity grey matter and centrum semiovale. Prominent VRS in the basal ganglia, subcortical white matter and centrum semiovale are a normal MR finding.

1.4.2.1.2 Subcortical lesions

Subcortical white matter hyperintensities (WMHs) are commonly identified on T2 weighted MR scans in healthy elderly patients. (29) The lesions have different aetiologies depending on location and configuration. Punctate lesions are characterized histologically by dilated perivascular spaces and perivascular gliosis, whereas more patchy lesions are associated with myelin pallor, dilated perivascular spaces and arteriosclerosis. Although early reports identified a history of ischaemic stroke as predictive for the presence of subcortical white matter lesions, recent investigations indicate the major correlative feature is age. Cognitive function is not related to the presence or absence of these lesions. (29)

1.4..2.1.3 Central lesions

WMHs in the corona radiata and centrum semiovale are typically found in a perivascular distribution. Patchy, more confluent WMHs are probably related to small-vessel atherosclerosis and myelin pallor. They are most commonly located in the watershed zones between the middle and anterior or the middle and posterior cerebral arteries; they rarely occur in the temporal or occipital subcortical areas. The extent and frequency of central WMHs are closely related to age Patients with hypertension, diabetes, hyperlipidaemia and cardiac disease have more WMHs compared to patients without these risk factors but this becomes statistically significant only in the eighth decade. (29)

1.4.2.1.4 Periventricular lesions

Several different types of periventriculat hyperintensities are seen on the T2 weighted MR scans in elderly people.

1.4.2.1.5 Perivascular spaces

These spaces increase in size and frequency with advancing age.

1.4.2.1.6 Sulci, Cisterns and Ventricles

Sulcal and cisternal enlargement are part of the normal aging process.

1.4.2.1.7 Cortical grey matter

Volume loss in the cortex with secondary enlargement of adjacent sulci and cisterns normally occurs with aging

1.4.2.2 Hypoxic –Ischaemic Encephalopathy (HIE)

Imaging manifestations of HIE vary with length and severity of the insult, patient age, individual cerebral circulatory patterns and the inherent vulnerability of certain anatomic regions and cell types to hypoxic-ischaemic injury. (30)

1.4.2.2.1 Premature infants

White matter of the developing brain is especially vulnerable to injury. The pathologic spectrum of lesions seen in HIE includes necrosis, gliosis and disturbances in myelination. Periventricular leukomalacia frequently occurs in premature infants and is probably caused by ischaemic infarction of the periventricular white matter, the vascular watershed zone in the developing foetus. Typical imaging findings include ventricular enlargement, irregular ventricular contours, reduced white matter volume and a moderately atrophic posterior corpus callosum. Occasionally there may be diffuse multifocal white matter lesions. (30)

1.4.2.2.2 Term infants

Ischaemic lesions are located predominantly in the cortex and subcortical white matter. The deep grey nuclei are also commonly affected.

1.4.2.2.3 Children and adults

HIE in these groups typically results in watershed infarction and bilateral selective neuronal necrosis within the globus pallidus, putamen, caudate nucleus, thalamus, parahippocampal gyrus, hippocampus, cerebellum and brainstem nuclei.

1.4.2.3 Subcortical Arteriosclerotic Encephalopathy (SAE)

This condition is often referred to as Binswanger's disease. (30) It is a slowly evolving dementia with focal deficits, hypertension and multifocal deep infarcts. It is related to multi-infarct dementia and may be part of the same entity. On MRI irregular areas of hyperintensity on T2 weighted images are seen in the white matter anterolateral to the frontal and occipital horns, the centrum semiovale, the basal ganglia and central portions of the pons. On CT scans, they appear hypodense. These areas in particular are vulnerable because of their arterial supply. One can consider the periventricular and deep cerebral white matter a watershed area because it is supplied by long noncollateralizing small-diameter arterioles that are extremely susceptible to reductions in blood flow. Also, these long perforating medullary arteries are especially sensitive to the effects of hypertension resulting in arteriolar narrowing and ischaemia. In addition, these areas in the brain lack the significant collateralization by the pial and leptomeningeal system seen in other parts of the brain. With aging, a progressive decrease in cerebral blood flow and increase in arteriosclerosis occur, which are accentuated by hypertension. The resulting ischaemia affects the susceptible deep white matter. The affected white matter in SAE has a consistent triad of demyelination, loss of axons and fibrous thickening of the wall of arteries. There are many hypotheses attempting to explain the pathophysiology of SAE. It is believed that SAE represents a vascular entity, and the microscopic changes in the vessels are identical to those of hypertensive patients with lacunar infarcts. Thus there is a relationship between systemic arterial hypertension and SAE, but it is still unknown if it is the sole cause. In SAE the frontal hyperintensities on T2-weighted sequences are

centred directly at the angles of the frontal horns, do not extend into the corpus callosum and spare the medial subependymal regions along the trigones and occipital horn.

1.4.2.4 Vasculitis

Central Nervous System (CNS) vasculitis refers to primary and secondary disorders of the CNS vessels. The common features are inflammation of the arteries and occasionally veins, of varying sizes, with injury to blood vessels, and consequent variable parenchymal ischaemia, infarction or haemorrhage. (31) CNS vasculitis may occur alone, or in association with known connective tissue diseases, systemic vasculitis, sarcoidosis, illicit drug abuse, malignancy and infection. See Table 1.4 for classification.

Classification of Central Nervous System (CNS) Vasculitis

Table 14 represents some of the causes of CNS vasculitis. (Adapted from: Lie JT. Classification and histopathologic spectrum of Central Nervous System Vasculitis. In: Younger D, editor. Neurologic Clinics Vasculitis and the Nervous System 1997, 15 (4) page 806)

Table 1.4
Primary CNS angiitis
Secondary CNS angiitis
Infection-related angiitis (bacterial, fungal, protozoal, mycoplasmal, rickettsial, viral)
Associated with systemic vasculitides or systemic diseases
Drug-associated anghtis
CNS vasculitis look-alikes and simulators

1.4.2.4.1 Primary CNS Angiitis (PACS)

This is an uncommon disorder and, to date fewer than 200 cases have been documented in the literature. (31) The disease occurs in patients of all ages and a higher incidence has been recorded in males. The definitive diagnosis of this condition requires biopsy or autopsy confirmation. Histologically, PACS affects the medium-sized and small arteries and arterioles of the meninges and cortex of the brain and only rarely the veins and venules. The diagnosis of this condition is based on history, presenting neurologic symptoms and signs, and consideration of other disorders that may present in a similar manner. Headache, encephalopathy and behavioural change, followed by focal deficits are common presenting features.

1.4.2.4.2 Secondary CNS Vasculitis

1.4.2.4.2.1 Collagen Vascular Diseases

The collagen vascular disorders associated with CNS vasculitis have distinctive clinical, laboratory and pathologic features. There is typical involvement of blood vessels, including the intracranial vessels. CNS involvement is significant in systemic lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis and sarcoidosis.

1.4.2.4.2.1.1 Systemic Lupus Erythematosus (SLE)

SLE is a complex multisystem disease that often has both central and peripheral nervous system manifestations. CNS involvement may be present in 60 to 75% of patients (32, 33). True vasculitis has recently been shown to be rare in the brains of patients with SLE (34). Vascular occlusion in SLE is however a relatively common finding and possible mechanisms include cardiogenic embolism and hypercoagulable states. Patients with SLE have a very high risk for recurrent stroke, with over 50% of patients with an initial stroke having one or more subsequent strokes. (35) This risk is present whether or not the patient has lupus anticoagulant or antiphospholipid antibodies. The angiographic spectrum ranges from normal or subtle small vessel disease to large vessel arteriopathy with bizarre fusiform aneurysms. MRI findings (29) in patients with nonfocal symptoms include multifocal areas of increased signal intensity in the subcortical white matter on T2 weighted images. Some lesions may enhance following contrast administration. Patients with SLE and symptoms of focal intracranial disease may have areas of increased signal intensity and atrophic changes in regions corresponding to major cerebral vascular distributions. Multifocal subcortical haemorrhages have also been identified.

1.4.2.4.2.1.2 Polyarteritis Nodosa (PAN)

This is a systemic necrotizing vasculitic disease with hyaline degeneration of small and medium-sized blood vessels. The arteritic lesions are present in various stages of evolution. Clinical CNS involvement occurs in about 25% of patients. (31). Single

and multiple strokes result from segmental narrowing, dilatation or occlusion of cerebral vessels as seen on angiography. Secondary cardiomyopathy and cardiogenic emboli are additional nonvasculitic mechanisms of CNS injury. MRI scans show nonspecific findings of diffuse cerebral atrophy and multiple high signal foci in the periventricular and subcortical white matter on T2 imaging.

1.4.2.4.2.1.3 Wegener's Granulomatosis

This is a nectrotizing granulomatous disease of the upper and lower respiratory tract, associated with systemic necrotizing arteritis of small arteries and veins and glomerulitis. Clinical and pathologic CNS involvement occurs in about 25% of patients. (36) Neurological involvement is generally secondary to contiguous invasion of nasal or paranasal granulomas and arteritis.

1.4.2.4.2.1.4 Sarcoidosis

Sarcoidosis involves the CNS as part of a systemic disease or alternatively it may be restricted to the brain or spinal cord in so called neurosarcoidosis. It is generally accompanied by basilar meningitis with inflammation of the meninges by noncaseating granulomas, and associated hypothalamic and pituitary dysfunction. MRI reveals enhancement of the meninges and multiple areas of infarction.

1.4.2.4.2.2 Infectious Causes

Diverse bacterial, viral, retroviral and fungal agents may be the cause of CNS vasculitis. Direct infection of blood vessels, humoral and cell-mediated immune damage, and immune complex formation account for most cases of infection-related CNS injury. (31) It is important to consider infection as the cause of vasculitis because neurologic improvement may follow antimicrobial therapy directed at the offending agent, with or without adjuvant immunosuppressant therapy.

1.4.2.4.2.2.1 Bacterial Agents

Acute Septic Meningitis

Acute bacterial meningitis leads to infection and inflammation of the meninges and subarachnoid spaces. Vascular involvement results from damage to arteries and veins as they traverse sites of inflammatory exudation. Angiography reveals vessel wall narrowing, dilatation, spasm, and distal branch occlusions. Venous phase films may reveal thrombosis and phlebitis of cortical veins and sinuses. Cerebral infarction occurs in approximately 10% of adults with bacterial meningitis, and in a quarter of neonates. (31) T2-weighted MR images show increased signal intensities in areas of ischaemia and infarction, similar to cerebritis.

Mycobacteria

Mycobacterium tuberculosis, the causative agent of tuberculosis is the commonest cause of chronic meningitis, and typically follows rupture of an old tubercle with the release of mycobacteria in the subarachnoid space. The thick gelatinous inflammatory exudate typically contains organisms, mononuclear cells, tubercles, and caseation necrosis, and settles at the base of the brain along cisterns, particularly in the Sylvian fissure, where arteritis can form along traversing blood vessels. Tuberculosis is an important consideration in a patient with chronic meningitis and known human immunodeficiency virus (HIV) infection because of the known heightened association, and the urgency of commencing chemotherapy.

Sprirochetes

Treponema pallidum is the causative agent of syphilis. Secondary vascular inflammation may follow syphilitic meningitis leading to arteritis, vascular occlusion, ischemia, and infarction of the brain or spinal cord. Meningovascular syphilis occurs years after initial infection, and is a common cause of stroke in young adults. Angiography and MRI most often reveal multifocal abnormalities in the distribution of the middle cerebral artery (MCA). The arteritis that occurs in this stage is probably mediated by spirochetal invasion of vascular endothelium. Vascular involvement is seen in tertiary syphilis decades later, but is not as prominent as the neuronal atrophy.

Borrelia burgdorfferi is the causative agent of Lyme disease and is transmitted by the bite of infected Ixodid ticks. Neurologic involvement occurs in up to 40% of patients at any stage of the disease. Stroke, transient ischemic attacks, subarachnoid hemorrhage, encephalopathy, and inflammation of meninges and CNS parenchyma can all occur. (37)

1.4.2.4.2.2.2 Viral Agents

CNS vasculitis can occur in the course of infection by varicella zoster (VZV) and retroviral infection. Hepatitis virus type A and C, are also associated with CNS vasculitis, but preferably affect the peripheral nervous system. Cytomegalo Virus (CMV) causes retinitis, meningoencephalitis, myelitis, and CNS vasculitis in association with HIV infection.

Herpes viruses

There are reports of vasculitis in association with primary VZV infection. Secondary VZV infection leads to a characteristic syndrome of contralateral hemiplegia and infarction of cerebral tissue in the territory of the ipsilateral carotid artery 2 to 3 weeks after VZV ophthalmic infection. The resulting arteritis leads to segmental narrowing, thrombosis, and beading along proximal branches of the anterior and middle cerebral artery on angiography. Pathologic studies in fatal cases show necrotizing granulomatous arteritis and occasional viral particles and antigens.

Retroviruses

Vasculitis also occurs in association with HIV infection. It may be the presenting symptom of HIV infection, or follow the acquired immunodeficiency syndrome (AIDS), but is most often associated with opportunistic VZV, CMV, tuberculosis, and syphilitic infection. Early invasion of the brain by the HIV is associated with T cell infiltration and a variety of other immune alterations. Cerebrovascular disease occurs in up to 30% of patients. (52) T2 weighted images best demonstrates the CNS lesions.

1.4.2.4.2.2.3 Fungi

Four fungal agents, aspergillus, candida, coccidioides, and mucormycetes are important CNS pathogens, especially in the presence of leucopaenia, sepsis, drug-induced or HIV-related immunosuppression and severe debilitation. These organisms have the capacity to invade arteries of the CNS in the course of disseminated infection and meningitis. Vasculitis may be acute, subacute, or a late complication of CNS infection. Cerebral infarction results from direct vascular injury leading to aneurysm formation, vascular thrombosis, endarteritis, and cerebral hemorrhage, or it may be due to microabscesses, or extension along contiguous sites of infection. Mucormycosis may be particularly aggressive in poorly controlled diabetes. There may be associated spread from sites of nasopharyngitis, oropharyngitis, and sinusitis to the cavernous sinus and int ıal carotid artery (ICA) leading to focal thrombosis and cerebral infarction, detectable by imaging studies.

1.4.2.4.2.3 Drug Effects

Histologically proven CNS vasculitis occurs with abuse and recreational use of amphetamines and cocaine. (39) Angiographic beading has been used as justification for the presence of vasculitis, but similar findings may follow vasospasm and cerebral hemorrhage. There is a model of methamphetamine-induced cerebrovascular injury in primates. CNS arteriopathy may follow a single intravenous bolus and persist for 2 weeks. Postmortem examination shows perivascular inflammation, in addition to variable subarachnoid hemorrhage, infarction of brain tissue, and microaneurysms. Non-vasculitic CNS injury in drug abuse may follow endocarditis owing to parenteral drug injections, which predisposes to embolic and haemorrhagic stroke, meningitis, mycotic aneurysms, and intracranial haemorrhage.

1.4.2.4.2.4 Malignancy

CNS vasculitis owing to necrotizing arteritis, granulomatous angiitis, or small vessel hypersensitivity angiitis, occurs with neoplasms, particularly lymphoproliferative tumors. High dosage irradiation for craniopharyngioma may present with angiographic abnormalities mimicking vasculitis. True CNS vasculitis occurs in up to one-third of patients with lymphomatoid granulomatosis. (31) Cerebral angiography reveals a pattern of narrowing consistent with angiitis. MR imaging reveals parenchymal lymphomatous mass lesions. The inflammatory destruction of arteries and veins is mediated by lymphocytoid and plasmacytoid cells, with rare granulomas

1.4.2.5 Hypertensive Encephalopathy

This is a syndrome characterized by a sudden sharp rise in blood pressure associated with headaches, nausea, vomiting and altered mental status. It can lead to stupor and coma. These symptoms of diffuse cerebral disturbance may be accompanied by focal or lateralizing neurologic signs, either transitory or lasting. There is rapid improvement after control of blood pressure. One theory is that the severe rise in blood pressure causes diffuse vasoconstriction of cerebral arterioles and spasm of these vessels. The resultant arteriolar necrosis and vascular permeability causes cerebral oedema. Vasoconstriction also leads to focal and diffuse areas of ischaemia and infarction. The basal ganglia and deep periventricular white matter owing to their tenuous blood supply, are predisposed to ischaemic necrosis in this hypoperfused state (30) CT scans show diffuse symmetric low-density areas mainly in the cerebral white matter causing compression of the ventricles, cisterns and sulci consistent with oedema. On follow-up CT scans, there is resolution of these findings consistent with oedema, rather than infarction. MRI has an increased sensitivity to water content and demonstrates to better advantage the altered hyperintense signal resulting from the oedema Infarcts and microhaemorrhages may occur during the course of this syndrome and are readily identified on MRI. Scattered cortical lesions occur in a watershed distribution and probably correspond to small infarctions.

1.4.2.6 Cerebral Amyloid Angiopathy (CAA)

Amyloidosis is a disease complex with a common unifying feature : tissue deposition of nonbranching fibrillar proteins that have the crystallographic characteristics of a beta-plated sheet. Three forms of amyloid deposit occur in the CNS as follows:

- The amyloid core of senile plaque.
- Cortical and leptomeningeal vessel wall deposits.
- Extension from small vessels into the surrounding brain parenchyma.

The latter two comditions are termed amyloid angiopathy (40).

CAA commonly results in superficial lobar haemorrhage. In contrast to hypertensive haemorrhages the haemorrhages in CAA are characteristically multiple, they tend to spare the basal ganglia and brainstem, and are located at the corticomedullary junction. Recently an association with CAA and leukoencephalopathy has been noted. (40). The white matter changes reported in CAA are distant to the areas of intracerebral haemorrhage. The blood vessels supplying the affected white matter did not contain amyloid. Microscopic review of the white matter revealed myelin loss, axonal degeneration and astrocytic gliosis, the triad seen with subcortical arteriosclerotic encephalopathy (SAE). Thus it is postulated that the amyloid deposition within the meningocortical vessels caused hypoperfusion of the deep white

matter with resultant ischaemic.demyelination. The most common sites involved were the centrum semiovale and deep periventricular regions, with sparing of the corpus callosum and internal capsule.

1.4.2.7 Eclampsia

This is a hypertensive disorder of pregnancy occurring after the twentieth week of gestation and is characterized by hypertension, proteinuria and seizures. The neurologic complications are varied and include headaches, visual disturbances, focal neurologic deficits and coma. The mechanism of central nervous system dysfunction is poorly understood. There may be several mechanisms at play including vasculopathy, perivascular microhaemorrhage, ischaemic brain damage, cerebral oedema and intracerebral haemorrhage. (41) Large haemorrhages can occur, but small intracerebral haemorrhages are more common. Pathologically one can see fibrinoid necrosis in the wall of the arterioles and small arteries. Angiograms of patients with eclampsia have demonstrated intracranial vasoconstriction. The most common area of involvement is the posterior cerebral circulation, where one finds cortical and subcortical white matter lesions in the occipital and posterior parietal lobes. The lesions are bilateral and symmetric and follow the gyri in a serpentine manner. Other areas that demonstrate hyperintense signal on T2 are the deep white matter and basal ganglia.

1.4.2.8 Antiphospolipid antibodies (APLA)

APLA are a heterogenous family of immunoglobulins, directed against phospholipids. The two most studied and recognized are anticardiolipin antibody (ACLA) and lupus anticoagulant (LA). LA is seen in 5% to 10% of patients with systemic lupus erythematosus, whereas patients with LA have a 34% chance of having systemic lupus erythematosus. APLAs can be found in patients with autoimmune disease however the majority of patients with these antibodies have no known recognized systemic disorder, and these patients are diagnosed with primary APLA syndrome. (42) The presence of these antibodies can lead to a multitude of abnormalities; the most common are systemic and cerebral thrombosis, foetal loss, thrombocytopaenia and neurologic syndromes which include stroke, encephalopathy, seizures and ischaemic optic atrophy and migraine. These antibodies are believed to have a direct cross reactivity with central nervous system phospholipids. Pathologic studies have shown thrombotic occlusion of medium-sized vessels without evidence of vasculitis or atherosclerotic disease. Radiographic findings in patients with APLA and neurologc symptoms include cerebral atrophy; small single or multiple hypodensities on CT in the cortical, periventricular and subcortical regions. MRI reveals vascular lesions, infarcts mainly in the cerebral white matter. Angiography reveals occlusions of arteries at unusual sites. (43)

1.4.2.9 Migraine

This condition and the radiologic abnormalities described in it have been discussed previously in the introduction. (See pages 3 to 11)

1.4.3 AIDS-Related White Matter Diseases

White matter disease is commonly seen on neuroimaging of AIDS patients. (44) 31% of patients have lesions on MRI that are completely confined to the white matter. (38) These abnormalities are most often diffuse but may be patchy, focal or punctate. There is often atrophy, characterized by sulcal enlargement and ventriculomegaly.

Listed below are some of the common causes of white matter disease in the AIDS population:

- **AIDS Dementia Complex**
- **Progressive multifocal leukoencephalopathy (PML)**
- **Cytomegalovirus**
- **Varicella Zoster Virus (VZV)**
- **Lymphoma**

1.4.3.1 AIDS Dementia Complex

Aetiology

This is progressive subcortical dementia. It is caused by CNS infection with the HIV virus itself.

Incidence

This condition eventually develops in up to 60% of AIDS cases late in the disease process.

Pathology

Atrophy is a prominent feature. Loss of axons, ill-defined areas of demyelination, gliosis and infiltration with multinucleated giant cells are seen.

Clinical Presentation and Natural History

Slowly or rapidly progressive dementia which may be accompanied by abnormalities of motor function are early presenting features. Inco-ordination of the limbs, ataxia of gait and impairment of smooth pursuit and saccadic are usually early accompaniments of the dementia. Increased tendon reflexes, primitive release signs, lower limb weakness progressing to paraplegia, bladder and bowel incontinence and mutism are prominent in the later stages of the disease.

Imaging

CT: Widened sulci and enlarged ventricles.

MRI: T2 images show ill-defined diffuse or confluent patches in the deep white matter. The frontal lobes are the most common sites. White matter lesions are usually bilateral but often asymmetrical. Grey matter is typically spared and mass effect is spared. These lesions do not enhance following contrast administration.

1.4.3.2 Progressive Multifocal Leukoencephalopathy (PML)

Aetiology

This is condition is caused by CNS infection with group B human papova viruses (principally the JC virus).

Incidence

This condition eventually develops in patients with a neoplasm or Chronic immunodeficiency state. It occurs in 1% to 4% of adult patients with AIDS. It is exceedingly rare in children with AIDS. (38)

Pathology

Widespread demyelinating lesions, mainly of the cerebral hemispheres but also of the brainstem and cerebellum. The spinal cord is rarely involved. The lesions vary in size and severity.

Clinical Presentation and Natural History

Personality changes and intellectual impairment may introduce the neurologic syndrome, which evolves over a period of several days to weeks. Typical manifestations include singly or in combination hemiparesis, quadraparesis, visual field defects, cortical blindness, ataxia, aphasia, dysarthria, dementia, confusional states and coma.

Imaging

CT: Widened sulci and enlarged ventricles.

MRI: T2 images show multifocal oval or round subcortical white matter hyperintensities in the parieto-occipital regions. Confluent white matter disease with cavitatory change is a late manifestation.

1.4.3.3 Cytomegalovirus (CMV)

Aetiology

This is a herpesvirus. AIDS patients are at risk of developing the disseminated form, normally associated with immunosuppression.

Incidence

CMV is latent in a large percentage of the adult population, with nealy 90% of adults having antibodies to CMV. (44)

Pathology

The hallmark is the owl's eye which may be difficult to find even at autopsy. This represents nuclear distension by viral inclusions with a surrouding halo. There may be subsequent extensive destruction of white and grey matter and ependyma.

Clinical Presentation and Natural History

Neurologic manifestations of CMV infection include acute or chronic meningo-encephalitis, cranial neuropathy, vasculitis, cerebral haemorrhage secondary to thrombocytopaenia, subarachnoid haemorrhage, retinitis, myelitis, brachial plexus neuropathy and peripheral neuropathy.

Imaging

CT: Atrophy is the most frequent finding. (44) Subependymal enhancing may be present.

MRI: Increased sensitivity in the detection of encephalitis. Atrophy is present. Increased signal intensity may be present in the periventricular white matter on T2 weighted images.

1.4.3.4 Varicella Zoster (VZV)

Aetiology

This is a herpesvirus which causes two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles).

Incidence

Reactivation herpes zoster or shingles is seen in 10 to 20% of patients with HIV infection. (45) White matter disease occurs in 2% or less of patients at autopsy. (38)

Clinical Presentation and Natural History

Neurologic manifestations of VZV infection include meningoencephalitis, cerebral vasculitis with hemiplegia (usually in association with opthalmic zoster), myelitis,

cutaneous lesions disseminated over several dermatomes and multifocal lesions of the white matter. In a cohort of patients with HIV infection, AIDS was noted to develop in 1% of the cohort per month following the diagnosis of localized zoster. Patients with HIV infection tend to have recurrences of zoster, with a relapse rate of approximately 20%. (38)

Imaging

CT: Atrophy is the most frequent finding.

MRI: Multifocal plaque-like areas of myelin loss occur near the grey-white junction. These lesions progress in size and eventually coalesce. T2 weighted images show multiple ovoid areas of high signal intensity in the deep and subcortical white matter.

1.4.3.5 Lymphoma (Primary CNS)

Incidence

This is the most frequent CNS neoplasm seen in the HIV-infected patient. (44) It was present in 0,6% of all AIDS cases reported to the Centre for Disease Control by June 30, 1989. (44) A strong male predominance was noted with only 5% of reported cases occurring in females.

Pathology

It is usually of B-cell origin. The most common types are diffuse large cell and diffuse immunoblastic lymphoma as well as small cell noncleaved. Lesions are often haemorrhagic and necrotic at pathology. They are usually centrally located, involving basal ganglia, thalamus, corpus callosum, cerebellar vermis and periventricular regions.

Clinical Presentation and Natural History

Patients present with focal neurologic deficits as well as confusion, lethargy, memory loss and B symptoms (night sweats and weight loss). Seizures are eventually present in one third of cases. Overall median survival is measured in months. (45)

Imaging

CT: Centrally located hyper and hypodense lesions which demonstrate dense enhancement with contrast are seen.

MRI: The lesions are isointense or hypointense to brain parenchyma on all sequences. The lesions have a low signal on T2 weighted images which is a fairly specific finding. Gadoliniun-DTPA injection demonstrates dense enhancement, either solid or ring-like on T1-weighted images. Ring enhancement is more often seen in necrotic lesions.

Single Photon Emission Computed Tomography (henceforth referred to as SPECT_Thallium): This can be used to distinguish lymphoma from toxoplasmosis. Neoplasms demonstrate uptake of thallium on nuclear imaging, whereas infections do not.

1.4.4 Viral and Post-Viral Demyelination

1.4.4.1 Infectious Demyelination

1.4.4.1.1 Subacute Sclerosing Panencephalitis (SSPE)

Aetiology

This is caused by the measles virus and is primarily seen in children.

Incidence

This is a rare condition now, due to the advent of childhood measles immunization. It was previously documented as occurring at a rate of one case per million children per year (45).

Pathology

Destruction of nerve cells, neuronophagia and perivenous cuffing by lymphocytes and mononuclear cells indicate the viral nature of the infection. In the white matter there is degeneration of medullated fibres accompanied by fibrous gliosis (sclerosing encephalitis). Eosinophillic inclusions, the histopathologic hallmark of the disease, are found in the cytoplasm and nuclei of neurons and glial cells.

Clinical Presentation and Natural History

SSPE affects children and adolescents for the most part, rarely appearing beyond the age of 18 years. The illness evolves in several stages. Initially there is a decline in proficiency at school, temper outbursts and other personality changes. These soon give way to a severe and progressive intellectual deterioration in association with focal or generalized seizures, widespread myoclonus, ataxia and sometimes visual disturbances. As the disease advances, rigidity, hyperactive reflexes, progressive unresponsiveness and signs of autonomic dysfunction appear. In the final stage the child lies virtually decorticated.

Imaging

CT: Normal, or there may be hypodense foci in the subcortical and periventricular white matter as well as the basal ganglia. Generalized atrophy is common.

MRI: T2 weighted scans show multifocal hyperintense foci in the cerebral white matter and basal ganglia.

1.4.4.2 Postviral Demyelination

1.4.4.2.1 Acute Disseminated Encephalomyelitis (ADEM)

Aetiology

This is an autoimmune response following an infection or vaccination. It occurs in several settings, as follows: (46)

- Shortly after a specific viral illness, especially exanthematous childhood diseases such as measles or chickenpox.
- Following a nonspecific, presumably viral upper respiratory infection.
- Following vaccination against rabies, diphtheria, smallpox, tetanus, typhoid or influenza.
- Spontaneously

Incidence and Age

The true incidence of ADEM is unknown. It occurs in all ages, although most reported cases are in children and young adults.

Pathology

Multiple perivascular inflammatory infiltrates are seen. These are associated with a zone of demyelination that follows the course of affected venules. Perivascular astrocytosis occurs as the disease resolves.

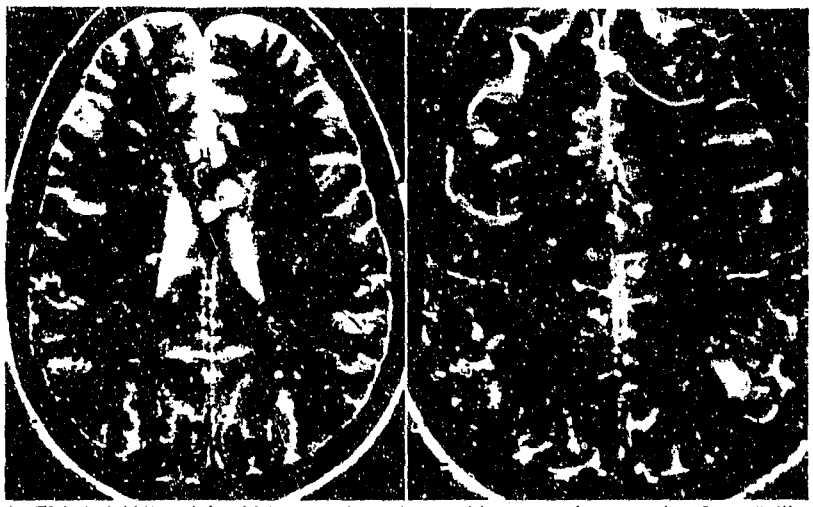
Clinical Presentation and Natural History

ADEM typically has an abrupt onset and a monophasic course. Neurologic symptoms characteristically begin 1 to 3 weeks after infection. The initial symptoms may be mild and include fever, headache and drowsiness. The clinical course is rapid. with development of multifocal symptoms that range from seizures and focal neurological deficits to coma and death. Some patients recover completely, whilst others may have permanent neurological impairment.

Imaging

CT: The scans may be normal, or shows nonspecific decreased white matter attenuation. The neurologic symptoms often precede the CT abnormalities.

MRI: T2 weighted scans show multifocal subcortical hyperintense foci. The deep white matter, brainstem and cerebellun can be affected. Lesions are widely distributed and typically bilateral but asymmetric. Occasionally, confluent disease with basal ganglia involvement occurs. ADEM is usually nonhaemorrhagic on MR. Some, but not all lesions enhance following contrast administration.



ADEM. Axial T2-weighted MR scans in a 20 year old woman taken 2 weeks after a flulike illness. (41)

1.4.5 Toxic Demyelination

This results from interaction of a chemical compound with the brain. A large number of chemicals are potential neurotoxins; some of the more important and common substances are listed below. Toxins cause temporary or permanent disturbance of normal brain function in several ways and include:

- Depletion of oxidative energy
- Nutritional deprivation
- Disturbances in neurotransmission
- Altered ion balance.

The toxins that act as potential neurotoxins include (29) :

Common: Alcohol

Uncommon: Osmotic demyelination, Hydrocarbons and other solvents, Cyclosporin toxicity, Methotrexate and radiation therapy.

Rare: Lead and mercury.

1.4.5.1 Chronic Alcoholism

Various specific processes related to ethanol intoxication affect the CNS. These include Wernicke encephalopathy, Marchiafava-Bignami disease and osmotic myelinolysis. Ethanol adversely affects vascular, glial and neural tissues. It also causes myelin degeneration. Nonspecific deep white matter and periventricular demyelinating lesions are seen on the MR scans of patients with chronic alcoholism. Demyelination is the main pathological finding in Marchiafava-Bignami disease and is the earliest, most constant lesion in Wernicke disease. (29)

1.4.5.1.1Wernicke encephalopathy (WE)

This is a disorder caused by nutritional thiamine deficiency, and occurs mainly in chronic alcoholics. The classic clinical triad consists of opthalmoplegia, ataxia and confusion. WE has a characteristic topographic distribution involving both grey and white matter. The periventricular regions, the medial thalamic nuclei, third ventricular floor and mammillary bodies are most frequently affected. MRI scans demonstrate hyperintense areas that surround the third ventricle and aqueduct on T2 weighted images. Studies obtained after vitamin therapy may show resolution of these abnormalities.

1.4.5.1.2 Marchiafava-Bignami disease

This is an uncommon disorder that is associated with chronic alcoholism. It is characterized by corpus callosum demyelination and necrosis although the cerebral hemispheric white matter and other commisural fibres may also be affected. Sagittal MR scans show callosal atrophy and focal necrosis as linear or punctate hypointense regions on T1 weighted images that become hyperintense on T2 weighted images.

1.4.5.1.3 Osmotic Demyelination (OD)

This is a toxic myelinolysis that classically occurs in alcoholic, malnourished or chronically debilitated adults. Over 75% of cases are associated with chronic alcoholism or rapid correction of hyponatremia, although other conditions such as hypernatraemia have also been implicated (29). Pathologically OD is characterized by myelin loss with relative neuron sparing. The central pons is the most common site. (29) CT scans are normal or disclose nonspecific hypodense areas. OD lesions are hypointense on T1 and hyperintense on T2 weighted MR scans. Enhancement following contrast administration is variable; some lesions enhance but most do not.



Osmotic Demyelination. Axial T1-weighted image demonstrates a focal area of decreased signal intensity within the pons. Two small hyperintensities within this abnormality represent the corticospinal tracts (arrows). Axial T2-weighted image demonstrates the hyperintensity in the pons with sparing of the descending tracts (arrows). (42)

1.4.5.2 Hydrocarbons and other Solvents

Myelin has a particularly high lipid content and a very slow metabolic turnover. All myelinated tracts are therefore especially vulnerable to lipid peroxidation and accumulation of toxic lipophillic substances. Organic compounds such as solvents and toluene cause multifocal white matter lesions that are detectable on T2 weighted MR scans.

1.4.6 Iatrogenic

1.4.6.1 Chemotherapy

Necrotizing leukoencephalopathy is the term used to describe diffuse white matter injury that follows treatment with chemotherapeutic agents, with or without associated radiation. Focal necrosis may also occur following chemotherapy. The incidence of injury following either chemotherapy alone or radiation therapy alone is low; when the two are used together, the incidence of injury increases markedly. The latent period between treatment and onset of symptoms is shorter after chemotherapy than after radiation. In one study, acute, clinically evident white matter injury occurred 1 to 3 weeks after treatment. (47) The pathologic findings in necrotizing leukoencephalopathy resemble those of radiation-related white matter necrosis and consist of axonal swelling, multifocal demyelination, coagulation necrosis, gliosis in the periventricular and centrum semiovale white matter. Axonal dysplasia is more

common than hyalinization and fibrinoid necrosis of the arterioles. Several types of cancer chemotherapy drugs, either alone or in combination with radiation therapy, have been strongly linked to leukoencephalopathy. The toxic effect of any single drug is difficult to establish because many effective cancer treatment regimens employ combinations of drugs with radiation. Clinically patients may become acutely symptomatic during the administration of chemotherapy but more commonly develop neurologic symptoms insidiously in the months or years following drug administration. Radiologic changes range from asymptomatic white matter hyperintensities seen incidentally at MR imaging to severe necrotizing white matter disease. Some of the drugs implicated in leukoencephalopathy are listed below:

Drugs causing Leukoencephalopathy

Cancer Chemotherapeutic agents: Methrotrexate, BCNU (Carmustine), L-asparaginase, Cytarabine, Cysplatin and Thiotepa

Immunosuppressive agents: Cyclosporin A and FK 506

Antibiotics: Amphotericin B

1.4.6.2 Radiation Injury

Three syndromes of radiation injury have been delineated : acute, early delayed and late delayed. (47) This classification is somewhat arbitrary, as overlap occurs between the clinical syndromes and pathologic findings. The acute reaction may begin during the latter part of a series of fractionated treatments or soon thereafter. There may be a seizure, a transitory worsening of the tumour symptoms, or signs of increased intracranial pressure. This syndrome has little prognostic significance. Although the condition is attributed to brain oedema, this is not visible on MRI scans. Its basis is unknown. The symptoms subside in days to weeks. In the early delayed syndrome the tumour symptoms may increase and by MRI the tumour mass may enlarge raising the possibility of further tumour growth, but again the symptoms usually resolve within 6 to 8 weeks. Postmortem examination discloses extensive demyelination, loss of oligodendrocytes beyond the confines of the tumour and varying degrees of tissue necrosis. Possibly dexamethasone hastens resolution. This condition can be associated with plaques of demyelination similar to multiple sclerosis. Late radiation injury occurs within 1 to 10 or more years after intensive radiotherapy [doses exceeding 50 Gy]. (47) This form is irreversible, progressive and sometimes fatal. It constitutes the major, dose-limiting complication of cerebral irradiation. There are two radiographic patterns of late radiation injury, which may occur separately or together: focal radiation necrosis and diffuse white matter injury. The basic pathology is probably the same in both instances, but the clinical and radiologic findings of the two syndromes differ sufficiently to warrant separate consideration

1.4.7 Trauma

Trauma is one of the most common nonvascular causes of nonvascular causes of focal white matter lesions. (29) Diffuse axonal injury results from axonal shearing caused by sudden acceleration-deceleration or angular rotation forces on the brain. It typically occurs with severe trauma, not minor injury, has a characteristic clinical presentation (immediate loss of consciousness without an intervening lucid interval) and is seen on T2 weighted MRI scans as multifocal hyperintensities in predictable locations. The grey-white interface, corpus callosum, internal capsule and brainstem are sites that are commonly affected. (29)

1.5 Migraine and White Matter Lesions

The clinical spectrum of migraine is much broader than just a specific type of headache. Migraine can arbitrarily be divided into "typical" and "atypical" variants. The typical syndrome of migraine consists of the classical and common migraine syndromes (described on page 3). Classical migraine is migraine associated with aura. The aura may occur independently of the headache. Common migraine refers to migraine without aura. Atypical or "symptomatic" migraine refers to a group of disorders in which the patient has migrainous headaches associated with other CNS conditions. These disorders include underlying arteriovenous malformations, brain tumours, cerebral aneurysms and Arnold-Chiari malformations. There exists also a group of conditions in which migraine and white matter lesions on MRI are prominent features of the disease entity. In this group are included CADASIL, MELAS, MERFF, Connective Tissue Diseases and MS.

CADASIL as described earlier (pages 18-19) is an inherited arterial disease of the brain which has recently been mapped to chromosome 19 The frequent abnormalities noted in a study of 148 patients (11) were recurrent subcortical ischaemic events (84%), progressive or stepwise subcortical dementia with pseudobulbar palsy (31%), migraine with aura (22%) and mood disorders with severe depressive episodes. (20%) The incidence of migraine in one large family presenting with the symptoms of CADASIL was recorded as 80%. (48) Verin et al, 1995 therefore proposed a new acronym "cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy and migraine (CADASILM)" to describe a phenotype of this

disease in which migraine is the dominant feature. The MRI features of CADASIL are suggestive of a diffuse white matter disorder and include multiple small subcortical infarcts which are symmetrical. (11)

MELAS (as described on pages 24-25) is characterized by recurrent attacks of prolonged migrainous headache, repeated vomiting in childhood, recurrent bouts of epilepsia partialis continua or convulsive status epilepticus and repeated cerebral infarctions. Eventually the affected individuals develop cortical blindness, cortical deafness and dementia. Cerebral catastrophies in these patients are often preceded by severe and prolonged migraine-like headache with nausea and vomiting. (49) The migrainous headache may occur in up to 73% of patients. (50) Infarctions in the grey and white matter are present on MRI. Specific areas may be more susceptible and these include the basal ganglia and thalami. The frontal lobes are relatively spared.

MERFF (described on pages 27-28) is another of the mitochondrial disorders which may have migrainous headache as a prominent symptom. This condition generally presents with progresssive myoclonic epilepsy or myoclonic ataxia which is elicitable by startle or limb movement. Hemicranial headache has been described in this condition but the frequency is unknown. (51) MRI findings include multiple regions of abnormal signal intensity and enhancement which reflect infarcts involving the cortex and adjacent white matter.

Migraine as a symptom in patients with MS is recognised. (52) Migrainous headaches may occur during and even herald the onset of relapse in MS The basis of migraine as

a symptom of MS is thought to be related to dysregulation of the serotonin system. The most common abnormal MRI finding in migraine is the presence of high signal white matter lesions (WML) on T2 images. The pathogenetic significance of these WML in migraine remains to be determined. The frequency of these brain abnormalities in studies fluctuates between 6% and 40%. WML have been reported with a similar frequency in migraine with aura and migraine without aura. WML have recently been distinguished on the basis of location:periventricular (PVF) i.e. contiguous to the ventricles and deep (DF) i.e. away from the ventricles. (53) Pavese et al, 1994 (17) found that their group of migraineurs only had WML of theDF type. Deep foci have previously (48) been noted to occur more often in individuals with cerebrovascular risk factors such as hypertension, diabetes mellitus and cardiovascular disease. These lesions are thought to be indicative of underlying cerebrovascular disease. It is possible therefore that the WML detected in migraineurs may be secondary to an underlying vasculopathy. Extensive WML as occur in diseases such as MS and CADASIL have not as yet been described in migraineurs.

CHAPTER TWO

AIMS

The aim of this study was to:

Evaluate migraine patients who were found to have extensive white matter lesions on MRI of the brain.

The patients were selected as follows:

- Diagnosis of migraine was made according to IHS criteria (see Appendix 1)
- Selection of patients for MRI was based on:
    - Focal symptoms/signs that were persistent or relapsing.
    - Atypical clinical presentations.
    - Suggestion of other pathology viz. MS or ADEM (see later)

CHAPTER THREE

METHODOLOGY

Patient Selection

This study was a retrospective analysis. Ethics clearance was obtained from the Ethics Committee of the University of the Witwatersrand. Patients with migraine who were randomly evaluated in terms of presentation were selected for the study only after MRI scans revealed extensive WML. The patients were recruited during the period 1992 to June 1998. They were identified on the basis of their focal signs and symptoms which were suggestive of a central remitting and relapsing illness. These patients were then evaluated as follows:

Evaluation of Migraineurs with Focal Deficits and WML on MRI

History and Clinical Examination (see Appendix 2)

Radiological Investigations

- CT scans of the brain.
- MRI scans of the brain.
- T1, T2, Proton density and Flair sequences were done.
- 4 vessel cerebral angiography. This was performed in patients in whom the investigation was clinically indicated in view of their vascular presentation..

Serological and Biochemical Investigations

- Serological testing for Syphilis
- Anti-nuclear Factor (ANF)
- Human Immunodeficiency Virus (HIV)
- Serum Angiotensin Converting Enzyme (sACE)
- Thyroid Function Tests (TFTs)
- Liver Function Tests (LFTs)
- Vitamin B12 level (B12)
- Folate level
- Serum Immunogloblulins
- Serum pyruvate and lactate levels

Cerebrospinal Fluid (CSF)

Consent was obtained for all CSF studies performed. The following investigations were carried out on the CSF:

- Microscopy, Culture and Sensitivity
- IgG/albumin index
- Oligoclonal antibody analysis
- Syphilis evaluation

Neurophysiology Tests

- Electroencephalography
  - A standard 16 channel EEG was performed on all patients using a NEC Multisync machine.
- Evoked Potentials
  - Visual and auditory brainstem evoked potentials using a Medelec Maestro 4ME machine were carried out in all patients.
  - Somatosensory evoked potentials were carried out only if a clinical indication existed.

Cardiology

Assessments were carried out by specialist cardiologists. The following procedures were performed:

- Electrocardiography
  - A standard ECG was performed on each patient.
- Echocardiography
  - A transthoracic echocardiogram was performed on each patient by a cardiologist.
  - Transoesophageal echocardiograms were performed if there was a clinical indication.

CHAPTER FOUR

DATA

AND

RESULTS

In this section the clinical and investigation profiles of each patient is presented. The case histories are described in detail. The data is then summarized in table form.

4.1 CASE PRESENTATIONS

4.1.1 Case 1

F.M. A 47 year old female.

Mrs. F.M. first presented to a neurologist in 1991. She had an event in which she developed vertigo, ataxia, dysarthria and diplopia. The attack lasted 45-60 minutes, and was followed by a severe headache. She was seen by her family practitioner who referred her to the neurologist. The neurologist detected no abnormalities on clinical examination and elected to do a CT scan of the brain. The scan was normal. She had none of the known risk factors for cerebrovascular disease and was referred to a cardiologist for further evaluation. Her cardiac assessment was normal. Specifically there was no mitral valve prolapse or other valvular lesions. She had a stress electrocardiogram (henceforth referred to as ECG) done which showed no evidence of underlying ischaemia. She also had carotid doppler studies done which were normal, in particular there were no plaques or turbulent flow evident. She was diagnosed as suffering from vertebro-basilar migraine.

Three months later she suffered another similar attack. Her symptoms persisted for 12-24 hours. She was seen by a second neurologist within 24 hours of the onset of her symptoms. The relevant neurological findings were skew deviation of the eyes and

nystagmus in the vertical and horizontal directions. She also had generalized hyper-reflexia. She had mild axial and appendicular ataxia. The remainder of her examination was normal. MRI scans of the brain were performed (see Table 4.4). The scans revealed white matter breakdown in the periventricular regions, corpus callosum and deep subcortical white matter. The radiologic features supported a diagnosis of Multiple Sclerosis and she was subsequently admitted for a five day course of intra-venous steroids. She recovered completely from this event.

She was reviewed by us three months later. She presented with recurrent migrainous headaches. Her migraine headaches began in childhood. Over the years they increased in frequency from once every 6-12 months to monthly attacks and even daily attacks during periods of stress.Her clinical examination was normal. There were no residual neurological deficits. Her MRI scans were reviewed and it was noted that in addition to the WML described previously she had involvement of the basal ganglia. It was also noted that there were no lesions in the brainstem or cervical cord. The lesions present were seen on T2 weighted images indicating either demylination or vasculopathy. She was then recruited into the study. She was investigated according to our protocol. She had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These tests were either normal or negative. (See Table 4.5) Her mitochondrial function was evaluated by checking serum pyruvate and lactate levels. These were normal on numerous occasions. A lumbar puncture was done and the cerebrospinal fluid (henceforth referred to as CSF) evaluation, including

oligoclonal antibodies were normal. An electroencephalogram (henceforth referred to as EEG) was done and revealed no abnormalities. Auditory and visual evoked potentials were tested and found to be normal.

She is currently on propranolol and amitriptyline , this is prophylaxis for her migraine. She uses Sumitriptan and/or Ergotamine during her acute attacks. She has not had any recurrences of the symptoms that she initially presented with i.e. vertigo, ataxia, dysarthria and diplopia, but continues to suffer migrainous headaches.
She has a brother who suffered an intracerebral hypertensive haemorrhage previously. MRI scans were done on him and they revealed no WML. She has an older sister, aged 56 years who is also a migraineur. A MRI was done on her sister and revealed no abnormalities.

F.M. has subsequently been seen by a neurologist in Toronto, Canada. He made a diagnosis of CADASIL in her. Genetic studies for the CADASIL genotype were however negative (report from attending neurologist). During her evaluation in Canada she had repeat MRI scans of her head and cervical spine. She had an angiogram done in Canada, which was reportedly normal. No new lesions were detected. She underwent a neuropsychiatric assessment which revealed no significant cognitive defects. She does however have emotional lability and an underlying depression.

4.1.2 Case 2

D. N. A 62 year old male.

His initial presentation to a neurologist was in 1991. He was evaluated for weakness, stiffness and cramps of his right leg. He did not have any neckache, backache, sensory or autonomic symptoms. The pain in his leg had evolved over a period of twelve months and was progressively deteriorating. He also suffered from migraine since childhood. Apart from the above symptoms he had a long-standing history of intractable migraine. He had been investigated previously for his migraine and reported that a CT scan of the brain had been done and was normal. His clinical examination on that occasion revealed a weakness in the L5/ S1 distribution in his right leg with an associated foot drop. His ankle reflex was absent on the right. He did not have any abnormalities of his left leg, upper limbs or cranial nerves. An MRI scan of his lumbar spine was done. There was a large cyst compressing the L5 root. He had the cyst removed by a neurosurgeon. According to the patient he felt well for at least 3 months following the surgery.

His symptoms recurred and became more noticeable a few months later. He began dragging his right foot again. He was seen by another neurologist approximately a year later. On this occasion it was noted that he had a spastic right-sided hemiparesis involving his right arm and leg. He also complained of continuous migrainous headaches which were unresponsive to therapy. The attending neurologist ordered a MRI scan of his brain. The scan revealed extensive lesions of the white matter

specifically in the periventricular, and subcortical regions and the corpus callosum. The neurologist suggested a diagnosis of chronic Multiple Sclerosis and also considered that the changes may be secondary to ischaemia. The patient was offered a trial of intra-venous steroids but opted instead for homeopathic medication.

He was initially seen by us a year later, 1994. He complained of right -sided weakness and stiffness with ongoing severe migraine. He also had features of an underlying depression and complained of mood swings. His general clinical examination was normal. The relevant neurological abnormalities were a spastic right-sided hemiparesis. A MRI scan of the brain and cervical spine was performed. The scan of the brain showed no new lesions when compared to the previous MRI. However, on review it was noted that there were no lesions in the brainstem, cerebellum and cervical cord. He did have mild cervical spondylosis. The WML were seen as increased signals on T2 imaging suggesting demyelination or vasculopathy. (See Table 4.4) He was therefore recruited into our study. He underwent investigations accoring to our protocol. . He had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition he had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These tests were either normal or negative. (See Table 4.5) His mitochondrial function was evaluated by checking serum pyruvate and lactate levels. These were normal on numerous occasions. He had a lumbar puncture done and the CSF evaluation including oligoclonal anitibodies was normal. His EEG was normal. Auditory evoked potentials were normal. The visual evoked potentials were normal. In view of the WML and his clinical presentation he

was treated with intra-venous steroids. This had no effect. He was diagnosed therefore as having a vasculopathy associated with migraine. A cerebral angiogram was subsequently done and this was normal.

He is currently being treated with amitriptyline, propranolol and flunarizine for the migraine. He continues to progress and on review shows marked spasticity affecting his right side.

In terms of his family history all his children are known migraine sufferers (2 sons, 3 daughters). All members of his immediate family were evaluated clinically and no neurological abnormalities were detected.). MRI scans were done on his eldest son and daughter, both severe migraineurs. These scans were normal.

4.1.3 Case 3

P. M. A 28 year old female.

Miss P.M. first presented to a neurologist in 1992. At that stage she developed an episode of sudden visual loss affecting her right eye. The attending neurologist diagnosed optic neuritis on the basis of a deafferented right pupil and papillitis. There were no other clinical abnormalities detected. She had a background history of migraine, diagnosed by her family practitioner when she was 14 years old. She apparently had a tendency for emotional disturbances, notably depression. She was treated with intra-venous steroids and recovered completely.

She was re-evaluated 6 months later. She complained at the time of migrainous headaches, visual abnormalities and depression. She was noted to have bilateral optic atrophy, but there was no pyramidal or cerebellar involvement. She was investigated at this stage. A CT scan of the brain and a lumbar puncture was done. The scan and CSF evaluation were normal. She was given a second course of steroids intravenously and apparently recovered completely.

She was seen by us a year later and her complaints were that of intractable migrainous headaches, poor visual acuity and mood swings. Her neurological examination revealed bilateral optic atrophy with an acuity of 6/12 bilaterally and a postural tremor. There were no other abnormalities. At this stage we elected to perform a MRI scan of the brain on the patient. The scans showed lesions in the deep and periventricular white matter, corpus callosum , centrum semiovale as well as the basal ganglia. There were however no lesions in the brainstem, cerebellum or spinal cord.

(See Table 4.4) She was recruited into our study at this stage. She was investigated according to our protocol. She had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These results were either normal or negative. A lumbar puncture was done and the CSF findings including oligoclonal antibodies was normal (as shown in Table 4.5). Her EEG was normal. Her visual evoked potentials were abnormally increased and her auditory evoked potentials were normal. A cerebral angiogram was done and this was normal.

She is currently on propranolol as prophylaxis. for her migraine.She uses sumitriptan and caffergot to treat her acute events. She has had numerous migraine attacks but there have been no new neurological deficits.

Her mother and father are both migraineurs. They have not suffered any neurological problems. MRI scans obtained on both her parents were normal. She has 2 younger siblings, both of whom suffer from migraine.

4.1.4 Case 4

N.S. A 40 year old male.

Mr. N.S. initially presented to a neurologist in 1996. His presenting symptoms were of an acute onset of weakness of his right leg, an associated right sided ptosis, a dysarthria and a feeling of unsteadiness. His symptoms began soon after an episode of a migrainous headache. He had a long-standing history of migraine and tension-type headaches. This however was the first episode in which his headache was associated with focal neurological symptoms. He consulted a general practitioner when his symptoms began . His general practitioner thought that he had suffered a cerebrovascular event and referred the patient to us for further evaluation. Mr. N.S. was very anxious and agitated on initial evaluation. His general examination was normal except for a mildly elevated blood pressure; the reading was 140/100. The relevant neurological findings were a right sided ptosis and a spastic right lower limb in which the tone and reflexes were significantly increased. His right upper limb was normal except for the presence of increased reflexes. The left upper and lower limbs were normal. He did not have any sensory or cerebellar abnormalities. In view of his clinical findings the patient was admitted for further investigations. A CT scan of the brain was done and this was normal. A lumbar puncture was done and the CSF evaluation (as noted in Table 4.5) was normal. We decided to do a MRI scan. The scan revealed extensive WML in the periventricular regions, corpus callosum and deep subcortical white matter. The WML were seen on T2 imaging. (See Table 4.4) The patient was therefore recruited into our study. He underwent investigations

accoring to our protocol. He had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition he had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These tests were either normal or negative. (See Table 4.5) An EEG and evoked potential studies were done and revealed no abnormalities. The patient was treated with intra-venous steroids. He improved steadily over the next few days. His headache subsided and the weakness in his leg improved. It is uncertain whether the improvement was spontaneous or a response to the steroids. The patient was followed up over a period of six months. There was a definite improvement in his ptosis but a minor residual deficit persisted. The tone in his right lower limb returned to normal; but his reflexes remained brisk.

He is currently on propranolol, amitriptyline and diclofenac as prophylaxis for his migraine. His acute attacks are treated symptomatically. The frequency of his migraine attacks have decreased considerably and he has been headache free for one year. He has not suffered any subsequent focal neurological events. The patient has been advised to take 75mg of acetylsalicylic acid daily.

4.1.5 Case 5

R.C. A 43 year old male.

Mr. R.C. first presented to a medical specialist in 1997. He had an episode of sudden-onset of headache associated with vertigo. He had a tension-type of headache which began sub-occipitally and radiated into his right orbit. The headache and vertigo persisted for several days with the vertigo outlasting the headache. The patient consulted an ear, nose and throat (henceforth referred to as ENT) surgeon because 12 years ago he had been treated for an episode of vestibular neuronitis. The attending ENT surgeon did not detect any abnormalities and subsequently referred the patient to a cardiologist. His cardiac evaluation which consisted of a stress test and an echocardiogram was normal. The patient improved and became asymptomatic a few weeks later.

Five weeks after his initial presentation his symptoms of headaches and vertigo recurred. The patient also noted a loss of balance and aggravation of his vertigo with certain movements of his head. He re-consulted the ENT surgeon who on this occasion diagnosed positional vertigo. The patient was treated with Promethazine and made a steady improvement.

The patient was dissatisfied with his diagnosis and consulted us in September 1997, three months after his initial event. Mr. RC had a long-standing history of migraine. His general clinical examination was normal except for a mildly elevated blood

pressure reading of 140/100. There was no postural hypotension. He had marked spasm in his sub-occipital muscles but there was no restriction in his range of neck movements. The only neurological abnormalities detected were non-sustained horizontal and vertical nystagmus and a mildly abnormal tandem gait. His reflexes were diffusely brisk. A Barany manouvre was performed and this was negative.

A CT scan had been done by the ENT surgeon and this was reviewed. There were no abnormalities. An MRI scan of the brain was performed. This revealed numerous sub-cortical, peri-ventricular and sentrum semiovale WML. The corpus callosum was also affected. Notably there were no lesions in the brainstem, cerebellum, cervical cord or basal ganglia. (See Figures 4.1-4.4 and Table 4.4) In view of the above findings the patient was recruited into our study. He underwent investigations accoring to our protocol.. He had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition he had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These tests were either normal or negative. (See Table 4.5) An EEG and evoked potentials were done which were normal. A lumbar puncture was not done because the patient refused to have the procedure performed. A cardiac assessment was repeated and showed no evidence of underlying chronic hypertension.

He is being treated with flunarizine and amitriptyline as prophylaxis for his migraine. His headaches have decreased in frequency. He has two sons who have chronic headaches. They have not been evaluated either clinically or radiologically.

Fig. 4.1 RC Axial Section

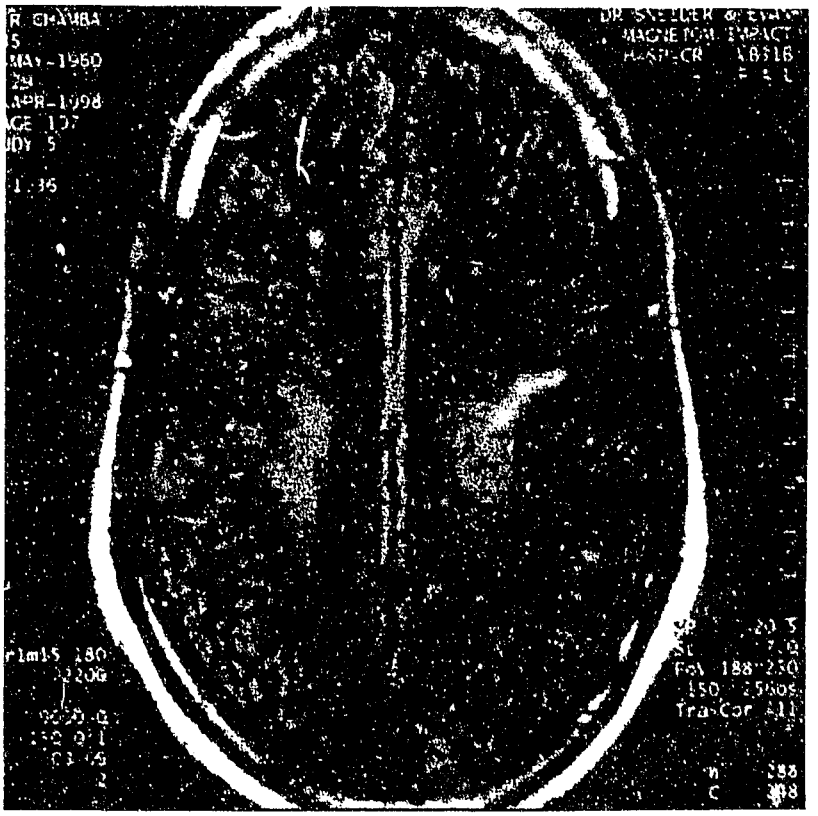


Fig. 4.2 RC Axial Section showing WML on T2 weighted image

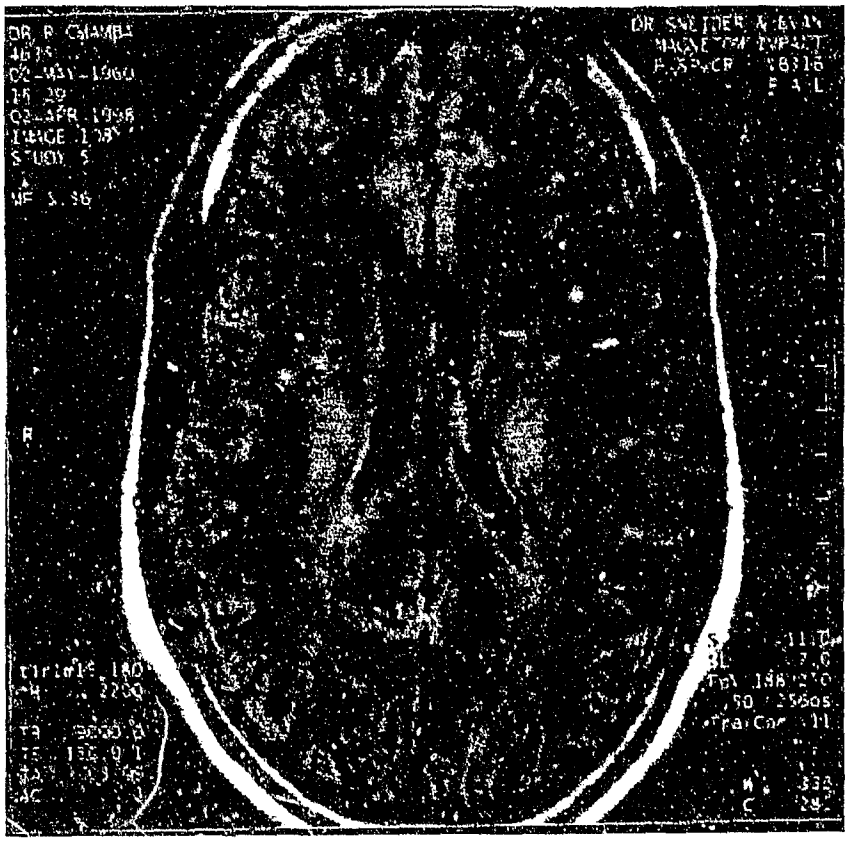


Fig. 4.3 RC Axial Section showing WML on T2 weighted image

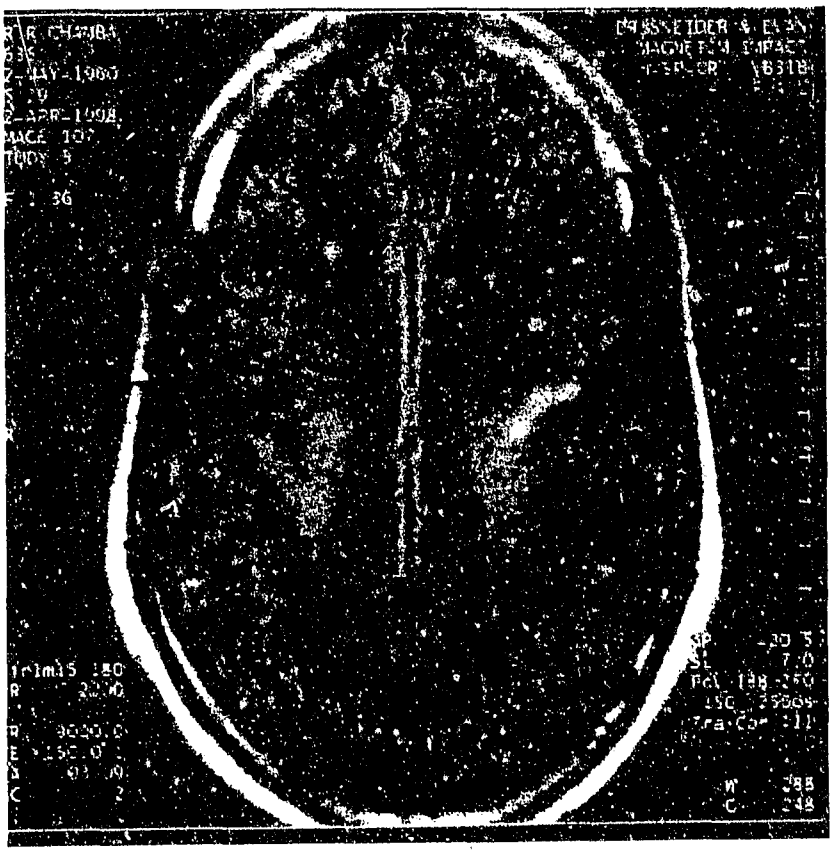


Fig. 4.4 RC Axial Section showing WML on T2 weighted image

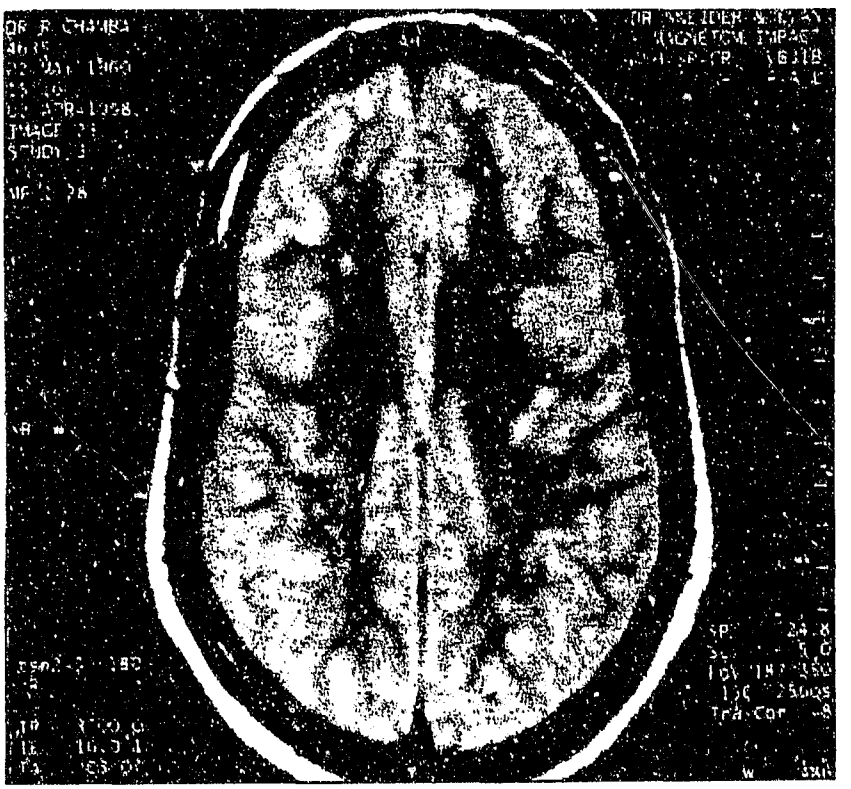


Fig. 4.5 RC Sagittal Section showing WML in the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.



4.1.6 Case 6

F.O. A 52 year old female.

Mrs. F.O. initially presented to us in 1992. Her initial complaints were of headache, fatigue and facial asymmetry. Her symptoms had been present for approximately six months prior to consultation. She had been referred to us by a psychiatrist who had been treating her for depression. Her headaches were fairly typical of a combination of migraine and tension-type headaches. The significant associated fatigue was unusual. Her general clinical examination was normal. Of relevance in her neurological examination was a left-sided upper motor neuron facial weakness and an increase in tone in her left upper and lower limbs associated with hyper-reflexia.. She had minimal weakness in her left arm which was only noted as a drift on presentation. A CT scan of the brain was done which was normal. A lumbar puncture was performed and the CSF evaluation was normal. The patient was assessed by a cardiologist and a stress test and echocardiogram were performed. These investigations were normal. In view of the above findings an MRI scan of the brain was done. The scan showed significant WML in the periventricular and sub-cortical regions and the corpus callosum. There were no lesions in the basal ganglia, brainstem, cerebellum or cervical cord. (See Table 4.4) The patient was therefore recruited into our study. She was investigated according to our protocol. She had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked.

These results were either normal or negative. (See Table 4.5) Her EEG was normal. Her visual evoked potentials were normal and her auditory evoked potentials were normal.

She is currently on flunarazine, amitriptyline and anti-inflammatories as prophylaxis for her migraine. Her acute attacks respond well to sumitriptan. She has not had any further episodes of focal neurological deficits. She has three daughters who possibly suffer from migrainous headache. None of her family members have been evaluated either clinically or radiologically.

4.1.7 Case 7

S.B. A 38 year old female.

Mrs. S.B. first presented to an opthalmologist in 1991. She complained of a sudden visual loss affecting her left eye. She was referred to a neurologist and a diagnosis of MS was made. The patient was pregnant at the time and was therefore not treated. During her pregnancy she suffered numerous attacks of migraine.

Two years later the patient developed numbness in her legs and hands. She complained of clumsiness and a feeling of loss of balance. She received a three day course of oral steroids from a neurologist. She had an incomplete recovery.
She presented to us in 1992. She complained of numbness, clumsiness and a left-sided weakness. Her symptoms had developed after two migrainous attacks. Her migraine attacks were usually mild and prior to her pregnancy in 1991 she had not had any associated focal neurological features. Her general examination was normal. Her pupils were equal in size and reactive to light.

She did however have a slight pallor of the left optic nerve head and decreased visual acuity on the left. The remainder of her neurological examination was normal An EEG was done, the recording was abnormal. There were sharp wave discharges at a frequency of 1-2Hz paroxysmally. There were no true epileptiform features. Her visual evoked potentials were abnormally increased on the left at 122m/sec. Her

auditory and somatosensory evoked potentials were normal. A MRI scan of the brain was done and this showed extensive WML in the periventricular and sub-cortical regions and the corpus callosum. There were no lesions in the brainstem, cerebellum or cervical cord. (See Figures 4.5-4.7 and Table 4.4) She was recruited into our study. She was investigated according to our protocol. She had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These results were either normal or negative. (See Table 4.5) A Gallium scan was done which was normal. A lumbar puncture was not performed because the patient refused to have the investigation performed. She refused further evaluation and therapy at this stage.

She has subsquently presented with similar symptomatology on two occasions; in 1995 and again in 1997. Each attack was preceded or accompanied by migrainous headaches. These attacks were not treated and the patient recovered completely. During her most recent episode she had a migrainous headache associated with metamorphopsia suggesting involvement of the occipital lobe. During this period her visual evoked potentials have remained persistently abnormal, but there have been no other abnormalities of evoked potentials. This patient was diagnosed as suffering from migraine with a vasculopathy.

She has a positive family history for migraine. Her maternal grandfather has severe migraine.

Fig. 4.6 SB Axial Section showing WML on T2 weighted image

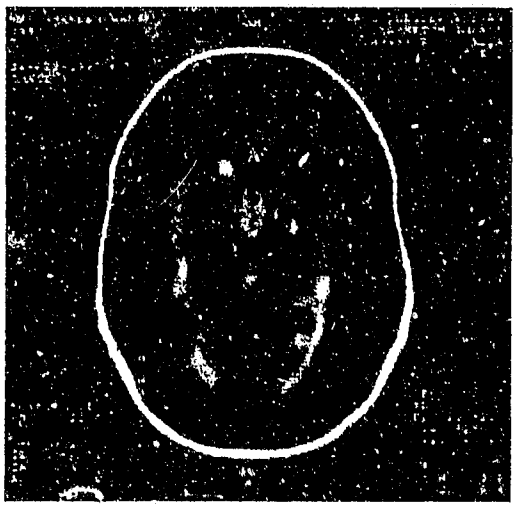


Fig. 4.7 SB Axial Section showing WML on T veighted image



Fig. 4.8 SB Sagi... Section showing WML in the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.



Case 8

Miss M.N. A 35 year old female.

Mrs. MN first presented to a neurologist in 1993. She had a long-standing history of severe chronic headaches. Her headaches began when she was twelve years old. Her headaches were migrainous in nature. She had an associated vertigo which often preceded the headache and in addition suffered from nausea and vomiting during the headache. She also occasionally suffered from episodes of loss of consciousness. These events were associated with the headache. In view of her syncope she was seen by a cardiologist who detected no abnormalities. She had also been evaluated previously by a neurologist. She had had an EEG done which was abnormal and it was therefore believed that her syncopal events may have been due to an underlying epileptic disorder. She was treated with Carbamazepine.

She was seen by us in February 1994. She was concerned about the frequency of her migrainous attacks and the associated vertigo and syncope. Mrs. MN was aware of some of the factors that precipitated her migrainous attacks and avoided known triggering factors. She had on history multiple features of a severe underlying depression. She was a moderately obese female. The remainder of her general clinical examination was normal. The only neurologic abnormality noted was marked spasm of her cervical muscles especially in the sub-occipital region. Of significance was the fact that her cranial nerves, motor, sensory and cerebellar examinations were normal. Her reflexes were symmetrically brisk. An EEG was done which was abnormal. There

were paroxysmal sharp wave discharges noted especially on hyperventilation. A MRI scan was performed and this revealed numerous sub-cortical white matter hyperintensities. Of significance there were no lesions seen in the brainstem, cerebellum or upper cervical cord.

Her clinical picture, EEG findings and scan results were considered and a decision was made to alter her therapy to sodium valproate and anti-inflammatories. She also received an analgesic/muscle relaxant combination to treat her neck pain and associated muscle spasm. She was reviewed on two further occasions; in July 1995 and in October 1996. She did not have any symptoms except the persistent headaches. Mrs. MN has a very strong family history of migraine. Her parents are both migraineurs and two of her three children suffer from chronic headaches. Her family members have not been evaluated by us.

Mrs. MN presented in March 1998 with an episode of severe headache, vertigo, ataxia and weakness of her left arm. On examination she had marked sub-occipital cervical muscle spasm, horizontal nystagmus and a mild ataxic hemiparesis of the left upper limb. She did not have any papilloedema or gross cerebellar signs. She was admitted to hospital for further evaluation. A MRI scan of the brain was done and this showed significant white matter signal hyperintensities in the sub-cortical and peri-ventricular regions especially in the left frontal area. There were no lesions in the sentrum semiovale, brainstem, cerebellum or cervical cord. The lesions had increased both in number and size when compared to the previous MRI. (See Figures 4.8-4.11 and Table 4.4) She was at this stage included into our study. She was investigated

according to our protocol. She had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These results were either normal or negative. (See Table 4.5) Her EEG was repeated and the abnormalities noted earlier were still present. She had evoked potential studies and a gallium scan done. These investigations were normal. During her hospital stay her symptoms resolved. She received a five day course of intra-venous steroids. Her previous therapy for migraine was re-institued as the patient had stopped taking her medication in 1996. She is currently stable except for a subjective weakness and dysesthesia in her left upper limb.

Fig. 4.9 MN Sagittal Section. There are no lesions seen in the cerebellum, cervical spine or brainstem. This is a T2 weighted image.



Fig. 4.10 MN Sagittal Section showing WML in the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.

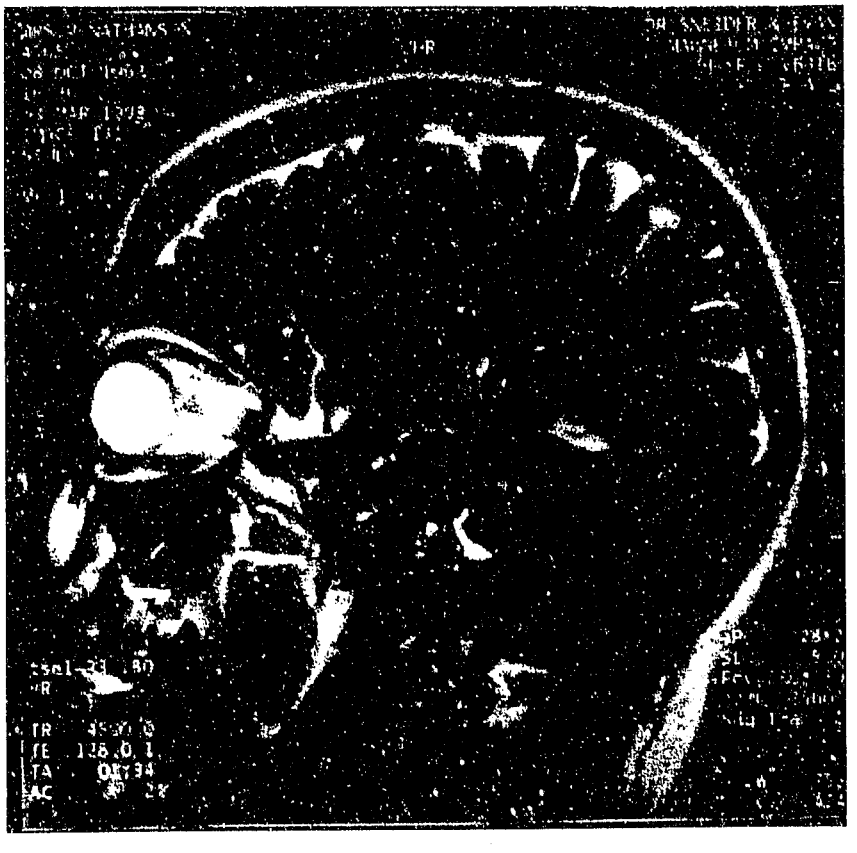


Fig. 4.11 MN Axial Section showing WML on T2 weighted image

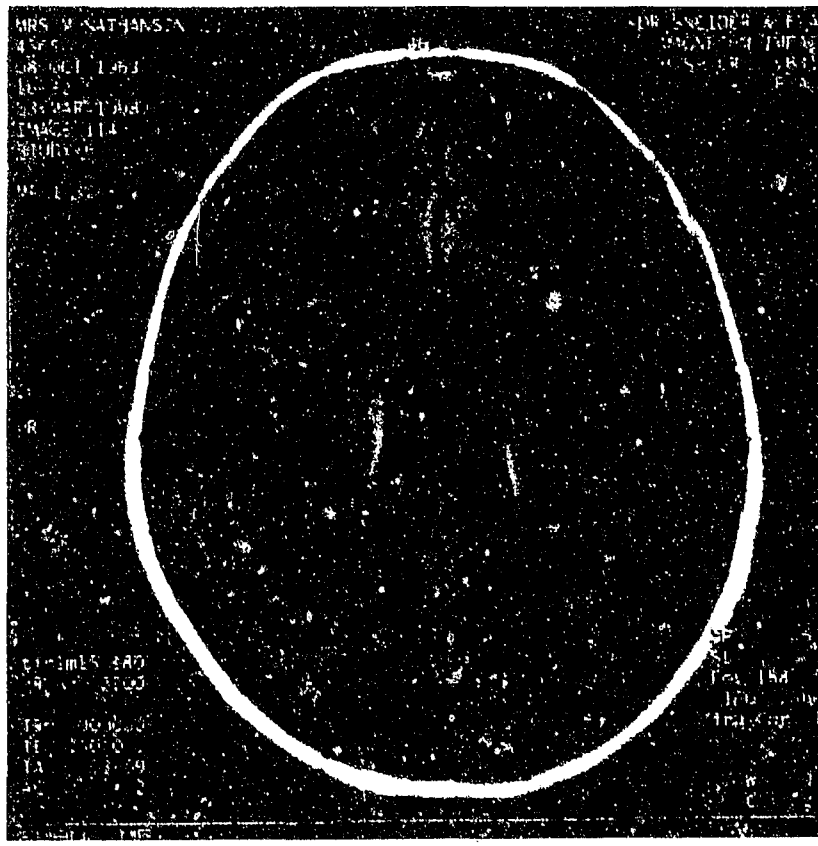


Fig. 4.12 MN Sagittal Section showing involvement of the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.



4.1.9 Case 9

C.C. A 41 year old female.

Mrs. C.C. initially presented to us in late 1992. Her neurological symptoms however dated back to October 1991. She had an episode during which her entire body became weak for 2-3 minutes. A month after this event she had an episode of right-sided weakness. This event was brief and there was complete resolution. Early in 1992 she had a prolonged episode of right-sided weakness. Her face, arm and leg were involved. She recovered completely from this without receiving any specific therapy. She was diagnosed by her general practitioner as having had a minor stroke. The only vascular risk factor that she had was that she was taking an oestrogen containing oral contraceptive pill.

Prior to her presentation to us she had an event during which she experienced right-sided weakness and clumsiness of her left hand. Her general examination was normal. She had on neurological examination a mild left-sided ataxia and a right hemiparesis. The patient was admitted for further investigation. A CT scan was done which was normal. A LP was done which revealed no abnormalities. The patient was investigated for a vasculopathy/vasculitis and the resultant tests were either normal or negative. A provisional diagnosis of cerebrovascular disease was made and the patient was started on Acetylsalicylic acid 150mg daily.

The patient was seen again by us in 1995. She presented with a history of severe left-sided migrainous headaches which were accompanied by dysesthesia of her left arm

and leg, dizziness and pre-syncopal events. Her general clinical and neurological examinations were normal. An EEG was done which revealed abnormal paroxysms of slowing in the delta range. There were no specific features to suggest an underlying epileptiform disorder. During this period no detailed investigations were done. The patient was treated with carbamazepine and acetylsalicylic acid.

The patient was seen again in May 1996. She complained of a strange feeling over the left side of her face associated with a severe left-sided headache and a mild earache. During this episode she indicated for the first time that she had been having recurrent headaches for many years. Her headaches began in childhood and had previously been diagnosed as migraine. Her migraine headaches were increased in frequency peri-menstrually. She did not take much cognisance of these headaches because they usually responded to simple analgesics. She now noted that her neurological symptoms were occurring in conjunction with her headaches. In view of her symptoms and normal clinical examination she had a CT scan of the cerebello-pontine angle region done. The scan was normal. A MRI scan of the brain was done which revealed extensive WML. The lesions were in the sub-cortical, periventricular regions and the sentrum semiovale. She also had lesions in the basal ganglia and the corpus callosum. (See Figures 4.12-4.15 amd Table 4.4) The patient was subsequently admitted for further investigations. She was at this stage included into our study. She was investigated according to our protocol. She had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These results were either

normal or negative. (See Table 4.5) A LP was repeated and the CSF evaluation was normal. Specifically the oligoclonal bands were negative. Visual and auditory evoked potentials were normal. Somato-sensory evoked potentials were not done. A gallium scan done was normal. She received intra-venous steroids for five days. She was treated with Amitriptyline, Clonidine and anti-inflammatories for her migraine. The patient was reviewed a month later. Her only symptom at this stage was a recurrent headache. On a further review two months later she was completely well.

In May 1997 the patient presented with an acute, severe migraine. She also complained of neckache and numbness of her left hand. Cervical spine X-rays and a paraspinal EMG with nerve conduction studies were done and helped to exclude a cervical radiculopathy. Evoked potentials were repeated. The brainstem evoked response was abnormal. The patient was admitted for a course of intra-venous steroids, following which she recovered completely. No further investigations were done at this stage. On discharge she was given low dose prednisone (5mg daily) and amitriptyline.

In August 1997 the patient had a severe attack of migraine which was associated with vertigo and ataxia. Examination at the time revealed nystagmus in the vertical and horizontal directions with marked appendicular ataxia. Her reflexes were diffusely increased. She complained of diplopia but did not have clinicl evidence of optic nerve damage. The patient was admitted and received a five day course of intra-venous steroids. A LP was repeated and the CSF evaluation was normal. Of note there were no oligoclonal bands present even during the acute event. A MRI scan of the brain

was repeated. The WML seen previously were still present. No new lesions could be identified. The patient was not given gadolinium. Following this attack she was given flunarizine, amitriptyline and low dose (5mg daily) prednisone. The patient has been reviewed on a 3-monthly basis and has not had any further attacks to date.

The patient has a positive family history in that her mother and eldest daughter are migraineurs. Neither of them have been evaluated.

Fig. 4.13 CC Sagittal Section showing WML in the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.



Fig. 4.14 CC Sagittal Section showing involvement of the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.



Fig. 4.15 CC Sagittal Section showing involvement of the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.

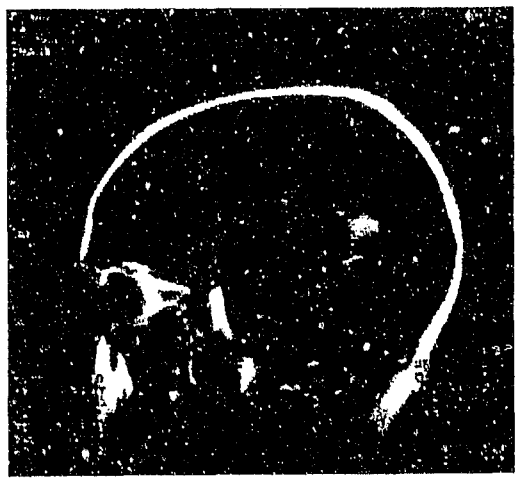
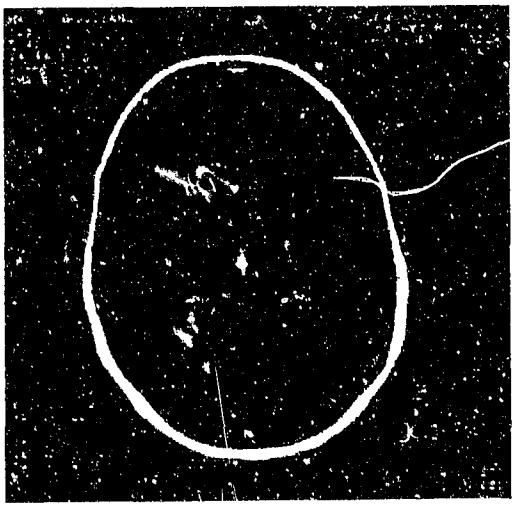


Fig. 4.16 CC Axial Section showing peri-ventricular WML on T2 weighted image



4.1.10 Case 10

Y.D. A 45 year old female.

Mrs. YD first presented to us in February 1998. She had an episode of sudden onset of left-sided weakness associated with a severe headache. She had been in an extremely stressful situation in the three month period preceding her presentation. She had a long-standing history of headaches which were migrainous in nature. She had been diagnosed as suffering from migraine as a child. She did not take any specific medication regularly and instead used various analgesic combinations intermittently. Her headaches had previously been investigated and a CT scan of the brain and an EEG had reportedly been normal.

Her general clinical examination was normal. The neurological abnormalities noted were an ataxic left hemiparesis, a left-sided intention tremor and an inability to tandem gait. The initial impression gained from her history and clinical examination was that she had probaly suffered a lacunar infarction in the pons. She was admitted for further evaluation. A CT scan of the brain was done which was normal. A MRI scan of the brain revealed numerous high signal intensities in the white matter on T2 imaging. The WML were present in the periventricular regions and around the occipital horns of both lateral ventricles. The brainstem, cerebellum and upper cervical cord regions were normal. (See Table 4.4) In view of the above findings the patient was recruited into our study. She was investigated according to our protocol. She had serological tests for syphillis, connective tissue diseases, human

immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These results were either normal or negative. (See Table 4.5) Of significance was the absence of oligoclonal antibodies. An EEG and evoked potential studies were normal. A cardiac evaluation which included an ECG and an echo were normal. She received a five day course of intra-venous steroids and recovered completely within two weeks.

She is currently on amitriptyline, propranolol and anti-inflammatories as prophylaxis for her migraine. She has not had any further episodes of focal neurological symptoms or signs.

Mrs. YD has a positive family history for migraine. Her mother and eldest son are migraineurs. Neither of them have been evaluated.

4.1.11 Case 11

M.C. A 49 year old female.

Mrs. M.C. presented to us on 18 April 1998. She had been referred to us by an ENT surgeon. Her medical history dated back several years, possibly to childhood. She had a history of dizzy spells which were usually followed by a headache. The headache she described consisted of a combination of migraine and tension-type components. Her acute complaint was that she had experienced ataxia during her most recent dizzy spell. She had recently had an event in which her "usual" symptom of vertigo was associated with ataxia, dysarthria and pre-syncope. The symptoms had been brief and resolved spontaneously. She initially went to her general practitioner who suggested that she may have had a transient ischaemic attack. She was referred to an ENT surgeon who found no abnormality and subsequently referred her to us. She did not have any risk factors on history for cerebrovascular disease. Her clinical examination was normal, of note there was no evidence of vascular disease. The only abnormality noted on neurological examination was the presence of nystagmus on lateral gaze. Her tone, power, reflexes and sensation were normal. Specifically there were no cerebellar abnormalities evident. The patient was investigated for vertebro-basilar ischaemia. Her vascular work-up and carotid doppler studies were normal. A cardiac evaluation which included a stress test and an echo was normal. X-rays of her cervical spine showed moderate degenerative disc disease but the spinal canal was normal. Evoked potential studies were normal. A lumbar puncture was not done because the patient refused to have the procedure performed. An EEG was done and this revealed no

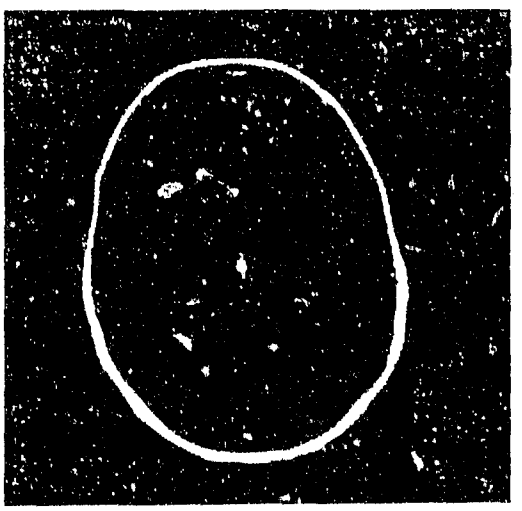
abnormalities. A MRI scan was done which showed extensive WML affecting the sub-cortical structures and the periventricular regions. There were no lesions in the basal ganglia, brainstem, cerebellum or upper cervical spine. (See Figures 4.16-4.17 and Table 4.4) The patient was recruited into our study. She was investigated according to our protocol. She had serological tests for syphillis, connective tissue diseases, human immunodeficiency virus and sarcoidosis. In addition she had thyroid function tests, liver function tests, a vitamin B12 level, a red cell folate level and serum immunoglobulin levels checked. These results were either normal or negative. (See Table 4.5) She did not receive intra-vascular steroids.

She is currently on acetylsalicylic acid 150mg daily and amitriptyline and flunarizine as prophylaxis for her migraine. She has a positive family history for migraine, her three sisters are migraineurs. None of her sisters have been evaluated by us for their headache.

Fig. 4.17 MC Sagittal Section showing involvement of the Corpus Callosum on T2 weighted image. There are no lesions seen in the cerebellum or brainstem.



Fig. 4.18 MC Axial Section showing peri-ventricular WML on T2 weighted image



Epidemiological Data

Table 4.1

	FM	DN	PM	NS	RC	FO	SB	MN	CC	YD	MC
Age	47	62	28	40	43	52	38	35	41	45	49
Sex	F	M	F	M	M	F	F	F	F	F	F
Race	ISA	ISA	BSA	BSA	ISA	ISA	ISA	MZ	MSA	MSA	MSA

Legend
- F = Female
- M = Male
- ISA = Indian Descent South African
- BSA = Black South African
- MSA = Mixed origin, South African
- MZ = Mixed origin, Zimbabwean

Presenting Features

Table 4.2

	FM	DN	PM	NS	RC	FO	SB	MN	CC	YD	MC
Headache	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Aura	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Stroke Like Event	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N
Cognitive Symptoms	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N
Medical History											
DM	N	N	N	N	N	N	N	N	N	N	N
HT	N	N	N	N	N	N	N	N	N	N	N
Cardiac Disease	N	N	N	N	N	N	N	N	N	N	N
Habits											
Smoker	N	N	N	N	N	N	N	Y	Y	Y	Y
Alcohol	N	N	N	N	N	N	N	N	N	N	N
Family History of Migraine	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

Legend
Y = Yes
N = No

Neurological Findings

Table 4.3

	FM	DN	PM	NS	RC	FO	SB	MN	CC	YD	MC
Higher Functions											
Memory Impairment	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Intelligence	N	N	N	N	N	N	N	N	N	N	N
Temporo-Spatial Ability	N	Y	N	N	N	N	N	N	N	N	N
Primitive Reflexes	N	N	N	N	N	N	N	N	N	N	N
Visuo-Spatial Ability	N	N	N	N	N	N	N	N	Y	N	N
Affective (Depression)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cranial Nerves	N	N	Y	Y	N	Y	N	N	N	Y	N
Motor System	N	Y	Y	Y	N	Y	N	Y	Y	Y	N
Sensory System	N	N	N	N	N	Y	N	N	N	N	N
Cerebellar System	N	N	Y	N	N	N	N	N	N	Y	N
Extra-Pyramidal System	N	N	N	N	N	N	N	N	N	N	N

Legend
Y = Yes, Abnormality Present
N = No, No Abnormality Present

Investigations

Table 4.4

	FM	DN	PM	NS	RC	FO	SB	MN	CC	YD	MC
MRI Findings (White Matter Changes)											
Periventricular	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sub-Cortical	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Corpus Callosum	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Basal Ganglia	Y	Y	Y	Y	N	N	Y	N	Y	N	N
Dawsons	Y	Y	Y	Y	?	Y	Y	N	Y	N	N
Brainstem	N	N	N	N	N	N	N	N	N	N	N
Cerebellum	N	N	N	N	N	N	N	N	N	N	N
Spinal Cord (Cervical)	N	N	N	N	N	N	N	N	N	N	N
EEG	N	N	N	N	N	N	Y	Y	N	N	N
Evoked Potentials											
AEP	N	N	N	N	N	N	N	N	N	N	N
VEP	N	N	Y	N	N	Y	Y	N	N	N	N
SSEP	ND	ND	ND	ND	N		N	N	N	N	N
Echocardiogram	N	N	N	N	N	N	N	N	N	N	N

Legend

Y = Yes, Abnormality Present
N = No, No Abnormality Present
? = Possible Abnormality Present
ND = Not Done

Laboratory Investigations

Table 4.5

	FM	DN	PM	NS	RC	FO	SB	MN	CC	YD	MC
CSF											
Protein	N	N	N	N	ND	N	ND	N	N	N	ND
Oligoclonal Bands	N	N	N	N	ND	N	ND	N	N	N	ND
IgG Index	N	N	N	N	ND	N	ND	N	N	N	ND
Serology											
WR	N	N	N	N	N	N	N	N	N	N	N
ANF	N	N	N	N	N	N	N	N	N	N	N
HIV	N	N	N	N	N	N	N	N	N	N	N
sACE	N	N	N	N	N	N	N	N	N	N	N
Chemistry											
TFTs	N	N	N	N	N	N	N	N	N	N	N
LFTs	N	N	N	N	N	N	N	N	N	N	N
B12	N	N	N	N	N	N	N	N	N	N	N
Folate	N	N	N	N	N	N	N	N	N	N	N
Serum Immunoglobulins	N	N	N	N	N	N	N	N	N	N	N
LCFAs	N	N	N	ND	N	N	N	ND	N	N	ND
Pyruvate and Lactate	N	N	N	N	N	N	N	H	N	N	N

Legend
Y = Yes, Abnormality Present
N = No, No Abnormality Present
ND = Not Done

Findings In Family Members

Table 4.6

	FM	DN	PM	NS	RC	FO	SB	MN	CC	YD	MC
Migraine	+	+	+	+	-	+	+	+	+	+	+
MRI Abnormalitics	-	-	-	ND	ND	ND	ND	ND	ND	ND	ND
Neurological Symptoms	+	-	-	-	+	-	Nil	Nil	N	N	N

Legend
" + " = Positive
" - " = Negative
ND + Not Done

Course Of The Illness

Table 4.7

	FM	DN	PM	NS	RC	FO	SB	MN	CC	YD	MC
Monophasic	+	-	-	+	-	-	-	-	-	+	-
Relapses	-	-	+	-	-	+	+	+	+	-	+
Chronic Progressive	-	+	-	-	+	-	+	-	+	-	+

Legend
" + " = Present
" - " = Absent

4.3 SUMMARY OF RESULTS OF 11 PATIENTS

There were eleven patients in our study. There was a female preponderance with eight of the eleven patients being female. The patients ranged in age from 28 to 62 years. Certain features were present in all our patients. They all had a history of migraine based on IHS criteria. They all suffered from depression but did not have any other cognitive symptoms. Each of our patients had had a focal neurological event which had been of acute onset. The nature of the event suggested either a vascular or a demyelinative process. The patients all had a positive family history for migraine.

The patients all had extensive WML on MRI scans. The lesions were predominantly in the periventricular and sub-cortical regions and the sentrum semiovale. Six of the eleven patients had lesions in the basal ganglia. None of the patients had lesions in the cerebellum, brainstem or cervical cord.

All the patients were investigated for a possible cause for these WML as per protocol. The work-up was negative. Two of the eleven patients had cerebral angiograms which were normal. The investigations done would not have excluded isolated CNS vasculitis as occurs with Primary CNS vasculitis because a brain biopsy is required to make this diagnosis. Mitochondrial function was assessed by checking pyruvate and lactate levels on several occasions. No muscle biopsies/DNA testing for mitochondrial deletions were done. No conclusive e clusion of mitochondrial disease could be made on the basis of the investigations done.

The differential diagnosis in the above patients therefore includes:

- Migraine with migrainous infarctions/ a vasculopathy of an undetermined cause.

- An acute remitting/ relapsing demyelinating event/ s as in MS or ADEM.

- A mitochondrial disorder with migraine and stroke-like events as occurs in the condition called MELAS.

- A CADASIL like disorder i.e. a sporadic or recessive form.

Our study protocol and results excluded some of the differential diagnoses. These patients do not have a Connective Tissue Disease, Syphillis, Sarcoidosis, Cardiac pathology or underlying infection with the Human Immuno-deficiency Virus all of which can explain the co-occurrence of migraine with WML. Each patient will now be discussed in terms of these differential diagnoses.

The eleven patients in this unusual series were evaluated with regard to their clinical presentation and the presence of white matter lesions on MRI. In each patient a differential diagnosis was considered as discussed above. This depended on their age, clinical presentation and course of their illness. The patients will be discussed in the order in which they were presented in the results section.

4.4 DISCUSSION OF CASES

4.4.1 Case 1

F.M. is a 47 year old female who has a very long history of migraine, the migrainous headaches beginning in childhood.

Her history and clinical presentation were highly suggestive of vertebro-basilar migraine. The WML noted on her scans are much more extensive than would be expected from migraine alone. MS is a consideration in this patient especially in view of her age, history and clinical features. Migraine, a prominent feature in this patient has been reported in up to 27% of patients with MS. (53) The normal evoked potential studies, CSF evaluations and the absence of WML in the cerebellum, brainstem and cervical spine argue against the diagnosis of MS. An underlying vasculitis or cardiac pathology were excluded on the basis of the normal serology and cardiac evaluation. Mrs. F.M. is the only patient in our study in whom genetic studies for the CADASIL genotype were done. The studies were negative and in the absence of a family history

of Cadasil make this condition unlikely. Her mitochondrial function tests were negative on numerous occasions. We would like to propose that the WML in this patient are due to a vasculopathy associated with her migraine.

4.4.2 Case 2

D.N. is a 62 year old male. This patient has chronic migraine and a progressive right-sided spastic hemiparesis and extensive WML on MRI. In view of his age we considered that his WML were an age-related phenomenon. Patients older than 75 years are reported to be at greater risk for the development of extensive WML (Hendrie et al). The WML could similarly be due to his migraine but their increased number and size are unusual. MS was considered by his attending neurologist initially but the normal CSF evaluation, evoked potential studies and the absence of WML in the cerebellum, brainstem and cervical spine regions argue against this diagnosis. Furthermore a repeat MRI scan showed no new lesions and his clinical progression is atypical of MS. A vasculitic work-up including cerebral angiography was normal making this condition unlikely. His cardiology work-up was similarly normal thereby excluding a cardiac source for the WML. His family history and clinical progression is atypical of CADASIL. His mitochondrial function tests were negative. We therefore consider him to have migraine associated with a vasculopathy.

4.4.3 Case 3

P.M. is a 23 year old female. Her relevant clinical features are a back-ground history of migraine, depression and optic atrophy. In addition to the above features she has extensive WML on MRI. In view of her age at presentation (22 years) she was extensively evaluated for the known causes of inherited white matter diseases. These investigations (as shown in Table 4.5) were either normal or negative. In addition her MRI findings were not consistent with any of the inherited white matter diseases described in the introduction. Her vasculitic work-up including cerebral angiography was normal making vasculitis an unlikely diagnosis. In view of her age and her presentation with optic neuritis MS was considered. Her CSF studies including oligoclonal antibodies were normal, the evoked potential studies were normal and she did not have any lesions in the cerebellum, brainstem or cervical cord. These features make a diagnosis of MS lessl ikely in this patient. A mitochondrial disorder could not be ruled out as she has not had a muscle biopsy but her serum pyruvate and lactate levels have been normal on several occasions. She has a positive family history for migraine but not for dementia or any of the other features described in patients with CADASIL. Furthermore MRI scans done in both her parents did not reveal any WML. The patient therefore has migraine associated with focal neurological deficits and extensive WML on MRI, the cause of which is not readily apparent. She therefore represents a patient with migraine and an associated vasculopathy.

4.4.4 Case 4

N.S. is a 40 year old male. The patient has a background history of migraine. He presented with a right-sided ptosis, dysarthria and weakness of his right lower limb following a migrainous headache. A MRI scan revealed extensive WML. His WML were not consistent with those that have been described to occur in migraine. MS seemed unlikely in the presence of a normal CSF evaluation, normal evoked potential studies and the absence of WML in the cerebellum, brainstem and cervical spine. He was investigated for a vasculitis but no evidence to suggest this was found. ADEM was considered in view of his presentation and possible response to steroids but the normal CSF findings and the absence of a preceding viral illness make this unlikely. His mitochondrial function tests were negative. There is therefore no readily apparent cause for his presentation of migraine, a focal neurological deficit and WML on MRI. His condition may be due to a combination of migraine and a vasculopathy.

4.4.5 Case 5

R.C. 43 year old male. Patient had a long-standing history of migraine and presented with two episodes of vertigo and nystagmus. His MRI scan revealed extensive WML. His late presentation (43 years), clinical progression and normal evoked potential studies made a diagnosis of MS unlikely. His vascular and cardiac work-up was normal making these conditions unlikely in him. His mitochondrial function tests were negative. The absence of a relevant family history and his presentation ruled against CADASIL. His WML are unlikely to be age-related. We have therefore to consider that this patients's focal neurological deficits and WML on MRI may be due to a vasculopathy related to his migraine.

4.4.6 Case 6

F.O. is a 52 year old female with a long-standing history of migraine and presented with features of a mild left hemiparesis. Her MRI revealed extensive WML in the periventricular and sub-cortical regions and the corpus callosum. She had a vasculitic work-up done which probably excludes this as a possible cause for her presentation. Her cardiac evaluation was normal as were her mitochondrial function tests. CADASIL seems unlikely in this patient in the absence of a relevant family history and the presence of a single stroke-like event. We considered benign MS as a possible diagnosis but her CSF evaluation, and evoked potential studies were normal. Furthermore she did not have any WML in the cerebellum, brainstem or cervical spine. We consider the most likely diagnosis in this patient to be migraine associated with a vasculopathy.

4.4.7 Case 7

S.B. 38 year old female. Patient has a background history of migraine and presented with focal neurological deficits on five occasions. A MRI scan done early in her evaluation revealed diffuse WML. Her clinical presentation of visual loss, parasthesiae and loss of balance is highly suggestive of MS. The presence of migraine headaches preceding the events is consistent with MS as are the persistently abnormal visual evoked potentials. The major findings which are inconsistent with the diagnosis of MS are the absence of WML in the cerebellum, brainstem and cervical spine and the complete resolution of her symptoms on each occasion despite her not receiving any specific therapy. Unfortunately a CSF evaluation could not be done as the patient refused to have a LP done. Her vasculitic work-up, cardiac evaluation and mitochondrial function tests were either normal or negative thus excluding these conditions. She did not have a family history suggestive of CADASIL. We assessed the patient as suffering from migraine with a vasculopathy.

4.4.8 Case 8

M.N. 35 year old female. Patient had childhood onset classic migraine. Her attacks were sometimes associated with weakness of her left arm. A MRI scan done showed extensive WML. Certain features in this patient namely her age, presence of migrainous headaches, her presentation with ataxia and monoparesis and her response to steroids are highly suggestive of MS. The normal CSF picture, normal evoked potentials and the absence of WML in the cerebellum, brainstem and cervical spine excluded MS. There was no family history to suggest CADASIL in this patient. Her mitochondrial function tests were negative making a mitochondrial disorder unlikely. The above findings made us consider migraine with vasculopathy a likely diagnosis.

4.4.9 Case 9

C.C. 41 year old female. The patient had childhood onset migrainous headaches that were on numerous occasions associated with focal neurological symptoms and signs. An MRI scan revealed extensive WML in the sub-cortical and periventricular regions and the sentrum semiovale. She was also noted to have lesions in the basal ganglia and corpus callosum. Our initial diagnosis in this patient was probable MS with migraine even though her CSF evaluation and evoked potentials were normal. She did respond to intra-venous steroids and recovered completely on each occasion. There were however certain features later in her clinical course which argued against MS. A repeat MRI showed no new lesions, specifically there were no lesions in the cerebellum, brainstem or upper cervical spine. She did have lesions in the basal ganglia which do not generally occur in MS. Her CSF evaluation was repeated and was consistently normal. Of note there were no oligoclonal antibodies even during the acute events. A CADASIL like disorder was considered but the family history made this unlikely. Normal mitochondrial function tests make an underlying mitochondrial disorder unlikely. In view of these findings we now believe migraine with a vasculopathy to be the diagnosis that best explains all her features.

4.4.10 Case 10

Y.D. 45 year old female. She has a long history of migraine and presented with a single episode of a focal neurological deficit. Her clinical presentation was suggestive of a vascular event. Her MRI picture however did not correlate with her clinical findings. She had diffuse WML in the sub-cortical and periventricular regions. These findings together with a normal vasculitic work-up and a normal cardiac evaluation ruled against a vascular basis for her presentation. The absence of MRI lesions in the cerebellum, brainstem and cervical spine and normal CSF evaluation coupled with normal evoked potential studies make MS unlikely in this patient. ADEM is a possibility in this patient and cannot be totally excluded even though her CSF studies were normal and there was no history of a preceding viral infection but this diagnosis does not take into account her chronic history of migraine. Her mitochondrial function tests were normal making an underlying mitochondrial disorder unlikely. She did not have a family history suggestive of CADASIL. She could therefore be considered to have migraine associated with a vasculopathy.

4.4.11 Case 11

M.C. a 49 year old female with childhood onset classic migraine. And a single episode of ataxia, dysarthria and pre-syncope. A presumptive diagnosis of vertebro-basilar ischaemia was made. She did not have any risk factors for vascular disease and her cardiac evaluation and carotid doppler studies were normal thus excluding a vascular cause for her presentation. A MRI scan revealed diffuse WML. There were however no lesions in the cerebellum, brainstem or cervical spine. In view of this MRI findings and the normal evoked potential studies we thought MS was unlikely in this patient. Her family history was not suggestive of CADASIL. Her mitochondrial function tests were normal. Our final assessment was therefore that the patient either suffered from vertebrobasilar migraine or migraine associated with vertebrobasilar ischaemia.

CHAPTER FIVE

DISCUSSION

5.1 AGING AND WML

Numerous studies have been done to evaluate the significance of the small, hyperintense foci seen on MR images of the brain in older patients. The results of these studies have been varied. Some of them have concluded that these changes are normal and merely part of an age-related phenomenon (54) whilst another has concluded that these lesions result from cerebrovascular risk factors (55).

The study by Hendrie et al, 1988 (54) looked at 27 healthy volunteer subjects aged 63 years to 83 years. The purpose of the study was to determine the presence and extent of increased T2 signal intensities on MRI scans and to correlate these lesions with cognitive function, cerebrovascular risk factors and the neurological examination. The presence, extent and severity of the increased T2 foci in the sub-cortical brain areas were rated in a blind fashion by two observers using a four-point scale described by Awad et al. (56) The grading was as follows:

- Grade 0: No foci of increased T2 signal.
- Grade 1: Foci confined to one lobe of the brain or to the posterior fossa.
- Grade 2: Multiple foci involving more than one lobe of the brain.
- Grade 3: Multiple confluent foci forming large patches.

The results of the MR scan ratings were that 16 (59%) of the patients had foci of increased T2 signal intensity on brain MR scans. Details of the results were: 2 patients had grade 1 lesions, 6 patients had grade 2 lesions and 8 patients had grade 3 lesions.

The authors did not find any significant differences between males and females and the presence of increased T2 foci. They found a significant difference in age for the rating categories. The mean ages of the four categories (grades 0 to 3) were 67.5, 73, 77 and 76.9 respectively. The most significant finding in this study was the correlation between advancing age and the presence and extent of WML. These results were even more striking if their subjects were divided into those who were 75 years and older and those under 75 years. 11 of 11 (100%) of subjects 75 years old and over had WML as opposed to 5 of 16 (31%) of subjects under 75 years old. The authors concluded that in their study of healthy elderly subjects the presence of increased foci of T2 high signal intensity was not correlated with cognitive performance or cerebrovascular risk factors. It was however strongly correlated with age.

Schmidt et al, 1992 (55) compared the prevalence of white matter hyperintensities (WMH) on MRI in two groups of patients. Their study group consisted of 133 consecutive stroke patients and the control group was 101 normal volunteers. The groups were comparable in age. In the study group 66 patients were male and 67 patients were female. In the control group 67 were male and only 34 female. They did MRI scans of the brain in all subjects. They graded the presence of WMH on the scans according to the following scheme:

- Grade 0: No lesions.
- Grade 1: Punctate lesions.
- Grade 2: Early confluent patterns.
- Grade 3: Confluent lesions.

Overall 59 (44,4%) of stroke patients and 48 (47,5%) of normal subjects had WMH on their scans. 27 patients (20,3%) had grade 1 WMH, 15 patients (11,2%) had grade 2 WMH and 5 patients ((3,8%) had grade 3 WMH. Significant findings were the correlation of WMH with age and diabetes mellitus. There was no significant association between WMH and the diagnosis of strokes. According to the authors the striking correlation of WMH with aging implied that age-related causative factors other than those responsible for atherothrombotic cerebral infarction play an important role in the pathogenesis of MRI white matter foci.

Braffman et al, 1998 (57) performed MRI scans of the brain on 23 formalin fixed brain specimens of patients 60 years and older at the time of death. They found 15 hyperintense white matter foci on T2 imaging These lesions were found in 7 brains. The sites and sizes of the lesions and correlating histopathological findings were as follows: (Table 5.1 adapted from Braffman et al).

Table 5.1

Age	Gender	Site	Size	Histopathology
78	F	R centrum semiovale	4 X 2	Infarct
70	F	(1) L occipital WM (2) Bifrontal WM (four sites)	10 X 10 2 X 2 (all)	Gliosis vs Infarct Infarct
75	M	Adjacent to temporal horn R lateral ventricle	10 X 10	Congenital variant of temporal horn Infarct
64	M	(1) L frontal WM & GM (2) L occipital WM	10 X 5 6 X 6	Brain cyst
61	M	L Centrum semiovale	4 X 4	Gliosis vs Infarct Demyelination
60	M	(1) Splenium, corpus callosum (2) L parietooccipal WM	4 X 4 25 X 5	Demyelination
63	M	Bilateral sentrum semiovale	3 X 3 4 X 3 3 X 3	No abnormality found

In order of decreasing frequency the lesions comprised infarction, infarction versus gliosis, demyelination, ventricular diverticulum and a brain cyst. In view of the above findings the authors concluded that the subtle lesions caused by vascular insufficiency and /or frank infarction account for the majority of hyperintense punctate WML seen in elderly patients.

Yetkin et al, 1993 (58) did MRI scans on 131 volunteers aged 40 to 87 years old. The purpose of their study was to survey variables in the subjects social, medical and surgical histories to identify those factors associated with focal hyperintensities in asymptomatic patients. Asymptomatic volunteers were examined with MR imaging of the head and questioned concerning smoking, chemical dependance, alcohol consumption, medical history, surgical history and other historical family and social

variables. Focal hyperintensities on MR studies were reviewed independently by 2 neuroradiologists. The foci were graded according to the number of small and large focal hyperintensities as follows:

- Grade 0: no focal hyperintensities.
- Grade 1: 1-3 small focal hyperintensities.
- Grade 2: 1-3 large focal hyperintensities.
- Grade 3: 1-3 small and 1-3 large focal hyperintensities.
- Grade 4: >3 small or large focal hyperintensities.
- Grade 5: >3 small and large focal hyperintensities.

The observers noted that 44 of the volunteers had focal hyperintensities and 87 did not. The number of focal hyperintensities varied according to the patients' age. The numbers were as follows: 0.3 per subject in patients 40-49 years old, 1.9 per subject in patients 50-54 years old and 2.1 per subject in patients greater than 55 years old. The grade of focal hyperintensities was therefore significantly associated with age. The other notable finding in this study was the association of focal hyperintensities with the use of anti-hypertensive medications. The large focal hyperintensities were 0.1 per subject in those with no history of using anti-hypertensive medications and 0.9 per subject in those with a history of taking anti-hypertensive medications. The authors concluded that focal hyperintensities were significantly related to age and the use of anti-hypertensive medications (probably indicating the presence of more severe or long-standing hypertension). The authors did not find any association between WMH and surgical procedures, surgical anaesthesia, history of head injury, loss of

consciousness, alcohol or tobacco abuse and the use of medications other than anti-hypertensives.

In conclusion the WML seen on MRI in the elderly probably represent ischaemia to the brain related to a vasculopathy, hypertensive or otherwise. In our series only 1 patient was older than 50 years of age. Mr. DN could be considered to have age-related WML but against this is the progressive nature of his neurological deficit and the lack of other deficits i.e. no history of strokes. He has severe symptomatic migraine at present. The clinical history of migraine is to abate with age. Therefore his clinical and radiological features cannot be explained solely on aging.

5.2 MIGRAINE AND MS

Migraine headaches may be the presenting symptom of relapse in and at times may even herald the onset of exacerbations of MS (52). Watkins and Espir, 1969 (53) looked at 100 consecutive patients with definite or probable MS. The purpose of this study was to determine whether patients with MS had a higher incidence of MS than the general poopulation. Their control group consisted of 100 hospital visitors matched for age and sex to the MS patients. Each group consisted of 64 females and 36 males. The patients ranged in age from 15 to 50 years. The authors reported an incidence of migraine of 27% in their patients compared to 12% of the control group. Of significance was the notable difference in the incidence of a family history of migraine in the two groups (20% of the MS patients compared to 10% of the controls). There was no explaination available for this finding.

Sandyk and Awerbach, 1994 reported 3 MS patients in whom migriane headaches developed during a period of relapse. They postulated that the emergence of the migraine headaches coincident with the onset of relapse implicated dysregulation of the serotonin system in the pathophysiology of MS.

In our study group 8 patients were female. They ranged in age from 28 to 52 years. Each of the patients had had an MS like event, and could conceivably be cases of migraine during an attack of MS as described by Sandyk and Awerbach. However, in the studies discussed above the patients had either definite or probable MS based on clinical and laboratory criteria. This is where our patients fell short as they did not

have a diagnosis of MS and did not have sufficient criteria i.e multiple clinical presentations, characteristic CSF findings, abnormal evoked potential studies and typical radiological features to make this diagnosis. Furthermore, they each had an established diagnosis of migraine as their principal diagnosis.

5.3 MITOCHONDRIAL DISORDERS AND MIGRAINE

Migraine headache is common in MELAS and in one study Hirano et al, 1992 (59) reported headache with nausea and vomiting in 73% of reviewed MELAS cases.

Klopstock et al, 1996 (50) noted some of the clinical features that were similar in both migraine and mitochondrial diseases i.e.

- Migrainous headaches with vomiting is a characteristic feature of MELAS and that hemicranial headache is present in MERFF
- Cerebral infarctions usually in the posterior cerebral regions are a main symptom of MELAS and that they may complicate migraine
- There is a mild bias towards maternal transmission in migraine.

In view of the above findings the authors decided to analyze the mitochondrial DNA in lymphocytes of 23 patients with classic migraine. Their patient group consisted of 16 females and 7 males. They ranged in age from 17years to 60 years. Their data showed that deletions of mitochondrial DNA and the most frequent point mutations of MELAS and MERFF syndromes did not occur in classic migraine. They specifically concluded that their data did not support the hypothesis that some cases of migraine may be monosymptomatic forms of a MELAS syndrome.

Koo et al, 1993 (24) reviewed 10 patients (5 females and 5 males) with MELAS. The age of symptom onset in their patients ranged from 3months to 12years. They found

that the patients who became symptomatic earliest presented with failure to thrive and feeding difficulties. Patients presenting later had migraine-like headaches as their predominant symptom at onset. Radiological scans in all their patients demonstrated progression of infarcts. In most patients (70%) the initial infarctions occurred in the occipital region. The infarctions involved both grey and white matter.

Montagna et al, 1988 (49) described 2 patients with characteristic clinical features of MELAS syndrome. They stressed the occurrence of severe migraine-like headaches with nausea and vomiting which preceded the cerebral infarctions. They surmised from their investigations that even mild complaints such as migraine, fatigability and sporadic seizures in relatives of patients with MELAS amy be an expression of mitochondrial dysfunction and represent an indication for muscle biopsy.

Our patients were different from those described in the studies mentioned above in that they did not present with recurrent stroke-like events, their age of onset was higher than the patients in the group described by Koo et al. (24) Furthermore, the patients in the above studies did not have lesions that were restricted to the white matter of the brain.

5.4 CADASIL AND MIGRAINE

Chabriat et al, 1995 11) studied 148 subjects belonging to 7 families by MRI and genetic linkage analysis. They found that 22% of their patients had classic migraine. They also noted that the migrainous attacks occurred earlier in life (38,1 years) when compared to the ischaemic events (49,3 years). They mention that CADASIL should be considered in patients with classic migraine whenever MRI reveals prominent signal abnormalities in the subcortical white matter and basal ganglia.

Verin et al, 1995 (48) evaluated 43 members of a large family presenting with symptoms of CADASIL. They found a very high incidence of migraine in their patients (80%) and suggested a new acronym CADASILM (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy with migraine) to describe their particular subvariety. They also proposed a chronological clinicoradiological staging that summarized the natural history of their particular phenotype. Their staging is described as follows:

- 'Stage I evolves from 20 to 40 years with migraine (with or without aura), and MRI investigations show well delineated lesions of the white matter".
- Stage II evolves between 40 and 60years with stroke-like episodes, bipolar or mono-polar like psychotic disorders, coalescent lesions of the white matter, and well delineated lesions of the white matter.

- Stage III includes patients over 60years old with subcortical dementia, pseudobulbar palsy, diffuse leukoencephalopathy and multiple well delineated lesions of the basal ganglia.

Verin et al, (48) mention that the mapping of Familial Hemiplegic Migraine and an autosomal dominant migraine with MRI WML to the same locus as CADASIL argues in favour of a relationship between migraine and CADASIL.

In a recently published study of a German CADASIL family Mellies et al, (59) studied 13 adult members of a 26 member four generation German family. Genetic studies strongly supported linkage in each patient to the CADASIL locus on chromosome 19p. The patients ranged in age from 30 to 59years. None of the patients ever had a transient ischaemic attack or stroke. The neurological examinations were normal except for higher function abnormalities in some of the patients and a gait abnormality in 2 patients. 4 patients had migraine with aura. 3 of these patients had late-onset migraine (in the fourth decade of life). 2 of the patients with migraine had progressed to develop dementia in their sixth decade. Neuropsychological testing disclosed cognitive impairment in a further three patients. 12 patients had MRI scans. Of these patients 6 had WML on their scans. The lesions were located in the periventricular white matter (all 6 patients) and the basal ganglia (4 off the 6 patients). In view of the above findings the authors concluded that the above family represented a new phenotype of CADASIL i.e. a phenotype characterized by the absence of focal neurologic symptoms and the presence of migraine and a progressive dementia only.

In our study 3 patient had WML with basal ganglia lesions and migraine. They fulfil some of the criteria mentioned above by Chabriat et al, 1995 (11) in their diagnosis of CADASIL. Only one patient however had genetic studies and these were negative. Against CADASIL is that the family histories and investigations in some of the family members were negative. Of interest is the fact that variants of CADASIL are being described. A recessive form of CADASIL could manifest as some of our patients have i.e. a migrainous family with a single member showing the phenotypic features of the disease. Sporadic occurrence of CADASIL should also be considered as a possible explaination for the negative family history and investigations in some families. Genetic linkage studies should be considered in our patients at some stage in an attempy to show linkage to the CADASIL locus

5.5 MIGRAINE AND WML

The reported findings in migraine from numerous imaging techniques (CT scans, angiography and position emission tomography) have been variable. MR imaging has emerged as a diagnostic tool with superb sensitivity in detecting early and subtle alterations in brain parenchyma. (14) The authors used this method to evaluate 24 patients clinically diagnosed as having migraine. In their series of 24 patients there were 8 males and 16 females. The patients ranged in age from 15 to 55years. 17 patients had classic or common migraine. 7 patients had complicated migraine.

- Classic migraine = severe, usually unilateral recurrent throbbing headache which is preceded by visual symptoms.
- Common migraine = severe, usually unilateral recurrent throbbing headache which is not preceded by visual symptoms.
- Complicated migraine = severe, usually unilateral recurrent throbbing headache which may or may not be preceded by visual symptoms. The headache is associated with neurologic deficits which are usually transient.

MRI showed parenchymal abnormalities in 11 (48%) of patients (7 with classic/common and 4 with complicated migraine). The lesions were well defined with prolonged T2 signal intensity. The lesions associated with common migraine were focal and predominantly in the periventricular white matter. The lesions were bilateral in 4 patients and unilateral in 3 patients. In the patients with complicated migraine large cortical abnormalities similar to infarcts were seen in 3 patients.

Multiple bilateral focal WML were seen in one patient. The lesions were mainly evident on T2 weighted studies. The focal periventricular WML were not necessarily associated with neurologic deficits. The cortical lesions were associated with clinical deficits. The authors could not correlate the lesions with histology and therefore could not infer their cause.

Pavese et al, 1994 (17) did MRI scans of the brain on 150 consecutive migraineurs and compared them to 50 controls. The aim of the study was to evaluate the presence of WML in a large group of migraineurs. In their group of patients83 had common migraine and 46 had classic migraine. There were 45 males and 105 females in the study group. In the control group there were 10 males and 40 females. Patients who were over 45years of age were excluded as were patients with cerebrovascular risk factors such as hypertension, diabetes, hyperlipidarmia, atrial fibrillation, anticardiolipin antibody syndrome and heavy tobacco smoking. They looked at the incidence of WML in their patients and distinguished two types of WML on the basis of location; periventricular (contiguous to the ventricle) and deep (far away from the ventricles). Their data showed an incidence of WML of 19,3% in their group of 129 migraine patients and only 2% in their control group. They found a similar incidence of WML in patients with classic migraine and patients with common migraine (21,7% vs 18%) and suggested that both forms of migraine are a different expression of the same disorder. They observed that their migraine subjects only had WML of the deep type. These lesions were localized in the sentrum semiovale. The lesions were ounctate in 24 of the 2 patients. 1 patient had early confluent lesions. The authors mention that deep foci have been shown to occur more commonly in old age and are

detected more often in individuals with cerebrovascular risk factors such as hypertension, diabetes mellitus and cardiovascular disease. (61) They postulated a vascular pathogenesis for the leukoareiosis found in migraine patients. In this study patients with cerebrovascular risk factors were excluded. The authors speculated that the presence of leukoareiosis in migraine might reflect the fact that migraine per se represented a cerebrovascular risk factor at least in a subgroup of patients.

Fazekas et al, 1992 (61) studied data from 38 migraine patients. The patients were referred for MRI scans as part of an evaluation for headaches. The purpose of the study was to look at the MRI results in different types of migraine headaches (migraine with aura, migraine without aura and basilar migraine). The study group consisted of 27 females and 11 males. The patients ranged in age from 17 to 59years. This group of patients was compared to a control group of 14 headaches free volunteers (age range 32 to 48years). Signal abnormalities were noted in 15 (39%) patients on MRI. In 10 patients the lesions were punctate WML on both proton density and T2 weighted images. The lesions were located in the sub-cortical or deep white matter. The prevalence of MRI abnormalities varied according to the type of migraine. PatIEnts without aura had the lowest incidence of MRI lesions (18%). MRI lesions were found in 38% of patients with basilar migraine and 53% of patients who had migraine with aura. The authors suggested thast the higher lesion prevalence in migraineurs with aura compared to migraineurs without aura was due to possible vascular stress during attacks.

Cooney et al, 1996 (16) did a retrospective review on MR imaging findings with respect to the presence of focal WMH in patients with migraine. The purpose of the study was to determine the frequency of MRI abnormalities and to see if any relationship existed between the frequency of MRI abnormalities and the patients age, sex, migraine type and other medical conditions (diabetes mellitus, hypertension, autoimmune disorders and demyelinating diseases). Their study population consisted of 40 males and 145 females. The patients ranged in age from 15 to 83years. In their study 16% of the patients were found to have WML on MRI. They demonstrated a statistically significant association between the presence of WML and both increased patient age and the presence of medical risk factors (listed above). They did not find any significant difference in frequency of WML with respect to sex, migraine subtype or duration of symptoms. They concluded that the vast majority of migraine sufferers especially those that were young and otherwise healthy, had normal white matter.

In summary the articles of the several authors discussed above indicate that WML do occur with varying frequency in migraine. The nature of these lesions is most probably vascular. Most patients have punctate lesions or slightly larger lesions. None of the papers discussed above describe lesions in the basal ganglia, brainstem or spinal cord. In our patients the most unusual aspect is the size of the lesions, their "deep" location as well as periventricular location and involvement in at least 6 patients of the basal ganglia. The events in each patient in our series was strongly indicative of an acute vascular or demyelinative event. The neurological deficits did not correlate on a 1 to 1 basis with the sites of the WML. This again points to

ischaemia or demyelination. It would therefore seem that we are describing a group of migraineurs with extensive WML unlike those described by other authors.

CONCLUSION

We have described in this study 11 patients with migraine who were found to have WML on MRI scans of their brains. The patients were extensively investigated but no apparent cause for their WML could be ascertained. It is our postulate that these lesions represent vascular events due to their location (so-called "deep" WML) and also the involvement of the basal gangli in some patients. The clinical profile of these patients may be summarized as one consisting of migraine with focal symptoms, cognitive symptom (depression) and sub-cortical WML on MRI scans of the brain. If, as we believe this is a distinct disorder the closest disease that it may resemble is the condition described as CADASIL. It would have to represent a recessive form or a sporadic occurrence of this disease. Genetic studies would be needed to confirm such a condition. At this point we can conclude that we have patients with migraine and a vasculopathy and we believe this to be a distinct subtype of migraine.

APPENDICES

Appendix 1

IHS CLASSIFICATION OF PRIMARY HEADACHES (62)

1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.2.1 Migraine with typical aura
1.2.2 Migraine with prolonged aura
1.2.3 Familial hemiplegic migraine
1.2.4 Basilar migraine
1.2.5 Migraine aura without headache
1.2.6 Migraine with acute onset aura
1.3 Ophthalmoplegic migraine
1.4 Retinal migraine
1.5 Childhood periodic syndromes that may be precursors to or associated with migraine
1.5.1 Benign paroxysmal vertigo of childhood
1.5.2 Alternating hemiplegia of childhood
1.6 Complications of migraine
1.6.1 Status migrainosus
1.6.2 Migrainous infarction
1.7 Migrainous disorder not fulfilling above criteria

2. Tension-type headache
2.1 Episodic tension-type headache
2.1.1 Episodic tension-type headache associated with disorder of pericranial muscles
2.1.2 Episodic tension-type headache unassociated with disorder of pericranial muscles
2.2 Chronic tension-type headache
2.2.1 Chronic tension-type headache associated with disorder of pericranial muscles
2.2.2 Chronic tension-type headache unassociated with disorder of pericranial muscles
2.3 Headache of the tension-type not fulfilling above criteria
3. Cluster headache and chronic paroxysmal hemicrania
3.1 Cluster headache
3.1.1 Cluster headache, periodicity undetermined
3.1.2 Episodic cluster headache
3.1.3 Chronic cluster headache
3.1.3.1 Unremitting from onset
3.1.3.2 Evolved from episodic
3.2 Chronic paroxysmal hemicrania
3.3 Cluster headache-like disorder not fulfilling above criteria

Appendix 2

History and Clinical Examination Questionnaire

- **EPIDEMIOLOGY**
  - Name
  - Age
  - Sex
  - Race

- **HISTORY**
  - History of the main complaint
  - Family History
  - Past Medical and Surgical History
  - Current Medication
  - Allergies
  - Habits

- **SYSTEMATIC ENQUIRY**
  - Neurological
  - Cardiovascular
  - Respiratory
  - Gastro-intestinal
  - Endocrine
  - Reticulo-endothelial
  - Gynaecological/Urological
  - Musculoskeletal
  - Skin
  - Psychiatric
  - Social Functioning
  - Other Features on History

- **EXAMINATION**
  - General Examination
    - Temperature
    - Blood Pressure: Supine Erect
    - Pulse Rate
    - Pulses and Bruits
    - Perfusion
    - Cyanosis
    - Pallor
    - Jaundice
    - Oedema
    - Clubbing
    - Hydration
    - Lymphadenopathy

- **SYSTEMATIC EXAMINATION**
  - Head and Neck
  - Respiratory
  - Cardiac
  - Abdomen
  - Urogenital
  - Musculoskeletal
  - Dermatological

- **NEUROLOGICAL**

- **Higher Functions**
  - Level of Consciousness
  - Appearance
  - Behaviour
  - Mood
  - Orientation
    - Time
    - Person
    - Place
  - Memory
    - Longterm
    - Intermediate Term
    - Short Term
  - Intelligence
    - Serial 7's
    - Level of Education
    - Judgement
  - Concentration
  - Mini Mental Score
  - Speech
  - Other

- **Cranial Nerves**
  - I
  - II
    - Pupils
      - Size
      - Shape
      - Reaction
      - Specific Abnormality
    - Visual Acuity
    - Visual Fields
    - Fundoscopy
  - III, IV and VI
    - Nystagmus
  - V
    - Corneal Reflex
    - Jaw Jerk
  - VII
  - VIII
  - IX and X
    - Gag Reflex
  - XI
  - XII

- **Motor System**
  - Involuntary movements
  - Bulk
  - Tone
  - Power
    - Upper Extremity
      - Shoulder
        - Abduction
        - Adduction
      - Elbow
        - Flexion
        - Extension
      - Wrist
        - Flexion
        - Extension
      - Intrinsic
      - Fingers
        - Flexion
        - Extension

- Lower Extremity
  - Hip
    - Abduction
    - Adduction
    - Flexion
    - Extension
  - Knee
    - Flexion
    - Extension
  - Ankle
    - Flexion
    - Extension
    - Inversion
    - Eversion
  - Toes
    - Flexion
    - Extension

- Refiexes
  - Upper Extremity
    - Pectoral
    - Triceps
    - Biceps
    - Supinator
    - Hoffmans
  - Lower Extremity
    - Adductor
    - Knee
    - Ankle
    - Babinski
  - Trunk
    - Abdominals
    - Cremaster

Sensation

- Parietal Lobe Testing
  - Dominant Lobe
    - Aphasia
    - Left-Right Discrimination
    - Finger Agnosia
    - Calculations
    - Alexia
  - Non-dominant Lobe
    - Extinction
    - Hemi-neglect
    - Dress Apraxia
    - Constructional Apraxia

- Light Touch
- Pin-prick
- Temperature
- Joint Position
- Vibration
- Pattern of Sensory Loss
- Specific Nerve Lesion
- Sensory Level

- **Cerebellar**
- **Gait**
  - Romberg's sign
- **Sphincter function**

- **Assessment**

REFERENCES

1. Goadsby PJ, Current Concepts of the Pathophysiology of Migraine. In: Mathew NT editor. Advances in Headache, Neurologic Clinics 1997 Feb;15(1):27-37.

2. Raskin N, Headache. In: Isselbacher K, Braunwald E, Wilson J, Martin J, Fauci A, Kasper D,editors. Harrison's Principles of Internal Medicine. 13nd ed. McGraw-Hill Inc. 1994: 65.

3. Raskin N, Headache. In: Isselbacher K, Braunwald E, Wilson J, Martin J, Fauci A, Kasper D,editors. Harrison's Principles of Internal Medicine. 13nd ed. McGraw-Hill Inc. 1994: 65-71.

4. Raskin N, Migraine and the Cluster Headache Synrome. In: Isselbacher K, Braunwald E, Wilson J, Martin J, Fauci A, Kasper D,editors. Harrison's Principles of Internal Medicine. 14nd ed. McGraw-Hill Inc. 1997:2307-310.

5. Rossor M, Headache, stupor and Coma. In: Walton J, editor. Brain's Diseases of the Nervous System. 10th ed. Oxford Medical Publications. 1993:12734.

6. Headache and other Craniofacial Pains. In: Adams R, Victor M, Ropper A, editors. Principles of Neurology, 6th ed. McGraw-Hill Inc. 1997:167-80.

7. Joutel a, Bousser MG, Biousee V, Labauge P, Chabriat H, Nibbio A, et al. A gene for familial hemiplegic migraine maps to chromosome 19. Nature Genetics 1993; 5:40-45.

8. Gardner K, Hoffman E. Current status of genetic discoveries in migraine: familial hemiplegic migraine and beyond. Current Opinion in Neurology 1998 (11) 3.211-5.

9. Jacome DE, Leborgne J. MRI Studies in Basilar Artery Migraine. Headache 1990; 30:88-90.

10. Merikangas KR, Genetics of migraine and other headache. Current Opinion in Neurology 1996 9:202-05.

11. Chabriat H, Vahedi K, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, et al. Clinical spectrum of CADASIL: a study of 7 families. The Lancet 1995;346: 934-39.

12. Zagami AS, Pathophysiology of migraine and tension-type headache. Current Opinion in Neurology 1994; 7: 272-77.

13. Cajade-Law A, Cohen J, Heier L. Vascular Causes of White Matter Disease. In: Edwards M, editor. White Matter Diseases Neuroimaging Clinics of North America. 1993 May; 3 (2): 374.

14. Soges L, Cascayorin ED,Petro GR, Ramachandran TS. Migraine: Evaluation by MR. American Journal of Neuroradiology, 1988, 9:425-429.

15. Igarishi H, Sakai F, Kan S, Okada J Tazaki Y. Magnetic resonance imaging of the brain in patients with migraine. Cephalalgia, 1991; 11:69-74.

16. Cooney BS, Grossman RI, Farber RE, Goin JE, Galetta SL. Frequency of magnetic resonance imaging abnormalities in patients with migraine. Headache, 1996 Nov, 36:10, 616-21.

17. Pavese N, Canapicchi R, Nuti A, Bibbiani F, Lucetti C, Collavoli P, et al. White matter MRI hyperintensities in a hundred and twenty-nine consecutive migraine patients. Cephalalgia 1994; 14:342-5.

18. Malandrini A, Carrera P, Ciacci G, Gonnelli S, Villanova M, Palmeri S, et al. Unusual clinical features and early brain MRI lesions in a family with cerebral autosomal dominant arteriopathy. Neurology, 1997; 48: 1200-203.

19. Tournier-asserve E, Iba-Zizen M, Romero N, Bousser M. Autosomal Dominant Syndrome With Strokelike Episodes and Leukoencephalopathy. Stroke, 1991; 22: 1297-302.

20. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton O, et al. Notch3 mutations in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a mendelian condition causing stroke and vascular dementia. Ann N Y Acad Sci, 1997; Sep, 826: 213-7.

21. Rubio A, Rifkin D, Powers JM, Patel U, Stewart J, Faust P, et al. Phenotypic variability of CADASIL and novel morphologic findings. Acta Neuropathol (Berl), 1997; Sep, 94: 3, 247-54.

22. Cajade-Law. Vascular Causes of White Matter Disease. In: Edwards M, editor. White Matter Diseases Neuroimaging Clinics of North America. 1993 May; 3 (2): 375.

23. The Inherited Metabolic Diseases of the Nervous System. In: Adams R, Victor M, Ropper A, editors. Principles of Neurology, 6th ed. McGraw-Hill Inc. 1997:928-87.

24. Koo B, Becker L, Chaung S, Merante F, Robinson B, MacGregor D, et al. Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-like Episodes (MELAS): Clinical, Radiological, Pathological and Genetic Observations. Ann Neurol 1993: 34:25-32.

25. Lee B. Magnetic Resonance Imaging of Metabolic and Primary White Matter Disorders in Children. In: Edwards M, editor. White Matter Diseases Neuroimaging Clinics of North America. 1993 May; 3 (2): 374.

26. Inherited Metabolic, White Matter and Degenerative Diseases of the Brain In Osborn A, editor. Diagnostic Neuroradiology, Mosby. 1994:716-47.

27. Multiple Sclerosis and Allied Demyelinative Diseases. In: Adams R, Victor M, Ropper A, editors. Principles of Neurology, 6th ed. McGraw-Hill Inc. 1997:902-20.

28. Farlow M, Bannin J. Clinical and Neuropathologic Features of Multiple Sclerosis In: Edwards M, editor. White Matter Diseases Neuroimaging Clinics of North America. 1993 May; 3 (2): 213-27.

29. Acquired Metabolic, White Matter and Degenerative Diseases of the Brain. In Osborn A, editor. Diagnostic Neuroradiology, Mosby. 1994;748-78.

30. Cajade-Law. Vascular Causes of White Matter Disease. In: Edwards M, editor. White Matter Diseases Neuroimaging Clinics of North America. 1993 May; 3 (2): 361-377.

31. Wynne P, Younger D, Khandji A, Silver A. Radiographic Features of Central Nervous System Vasculitis. In: Younger D, editor. Neurologic Clinics Vasculitis and the Nervous System 1997; 15 (4) 779-801.

32. .Hahns BH. Systemic Lupus Erythematosus. In: Isselbacher K, Braunwald E, Wilson J, Martin J, Fauci A, Kasper D,editors. Harrison's Principles of Internal Medicine. 13nd ed. McGraw-Hill Inc. 1994; 1643-48.

33. Cerebrovascular Diseases. .In: Adams R, Victor M, Ropper A, editors. Principles of Neurology, 6th ed. McGraw-Hill Inc. 1997:858-9.

34. .Hanly JG, Walsh NMG, Sangalang V. Brain Pathology in systemic lupus erythematosus. J Rheumatol 1991; 71 416-22.

35. .Futrell N. Inflammatory vascular disorders: diagnosis and treatment in ischaemic stroke. Current Opinion in Neurology 1995; 8:55-61.

36. .Nishino H, Rabino FA, DeRemee RA. Neurological Involvement in Wegener"s Granulomatosis: An analysis of 324 consecutive patients at the Mayo Clinic. Annals of Neurology, 1993 January, 33(1): 4-9.

37. .Stroke. In Osborn A, editor. Diagnostic Neuroradiology, Mosby. 1994:331-94.

38. Fauci AS, Clifford Lane H. Human Immunodeficiency Virus (HIV) Disease: AIDS and Related Disorders. In: Isselbacher K, Braunwald E, Wilson J, Martin J, Fauci A, Kasper D,editors. Harrison's Principles of Internal Medicine. 13nd ed. McGraw-Hill Inc. 1994: 1588.

39. Merkel P, Koroshetz J, Irizanry M, Cudkowicz M. Cocaine Associated Cerebral Vasculitis. Seminars in Arthritis and Rheumatism, 1995 25(3): 172-83.

40. Intracranial Haemorrhage. In Osborn A, editor. Diagnostic Neuroradiology, Mosby. 1994.154-96.

41. .Richards A, Graham D, Bullock R. Clinicopathological study of neurological complications due to hypertensive disorder of pregnancy. JNNP, 1988 51:416-21.

42. Weksler B. Haematologic disorders and ischaemic stroke. Current opinion in Neurology 1995; 8:38-44.

43. Brey RL, Hart RG, Sherman DG, Tegeler CH. Antiphospholipid antibodies and cerebral ischaemia in young people. Neurology 1990;40:1190.

44. .Whiteman ML, Post MJ, Bowen BC, Bell MD. AIDS-Related White Matter Diseases In: Edwards M, editor. White Matter Diseases Neuroimaging Clinics of North America. 1993 May; 3 (2):331-54.

45. .Viral Infections of the Nervous System. .In: Adams R, Victor M, Ropper A, editors. Principles of Neurology, 6th ed. McGraw-Hill Inc. 1997:743-73.

46. Infections of the Brain and Its Linings. In Osborn A, editor. Diagnostic Neuroradiology, Mosby. 1994:673-713.

47. .Rowley HA, Dillon WP. Iatrogrnic White Matter Diseases In: Edwards M, editor. White Matter Diseases Neuroimaging Clinics of North America. 1993 May; 3 (2):379-400.

48. Verin M, Rolland Y, Landgraf F, Chabriat H, Bompais B, Michel A, et al. New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent feature. JNNP 1995; 59(6):579-85.

49. Montagna P, Gallassi R, Medori R, Govoni E, Zeviani M, Di Mauro S, et al. MELAS syndrome: Characteristic migrainous and epileptic features and maternal transmission. Neurology 1988; 38:751-4.

50. Klopstock T, May A, Seibel P, Papagiannuli E, Diener HC, Reichmann H. Mitochondrial DNA in migraine with aura. Neurology 1996; 46:1735-38.

51. Hammans SR, Sweeney MG, Brockington M. The mitochondrial DNA transfer RNA A-G mutation and the syndrome of myoclonic epilepsy with ragged red fibres (MERFF). Brain 1993; 116 617-32.

52. Sandyk R, Awerbach G. The co-occurrence of Multiple Sclerosis and Migraine Headache: The Serotoninergic Link. International Journal of Neuroscience 1994; 76(3-4):249-57.

53. Watkins S, Espir M. Migraine and multiple sclerosis. JNNP 1969; 32: 35-37.

54. Hendrie HC, Farlow MR, Austrom MG, Edwards MK, Williams MA.. Foci of increased T2 signal intensity on brain MR scans of healthy elderly subjects. *AJNR*. 1989; 10:703-707.

55. Schmidt R, Fazekas F, Kleinert G, Offenbacher H, Gindl K, Payer F, et al. Magnetic Resonance Imaging Signal Hyperintensities in the Deep and Subcortical White Matter. Arch Neurol 1992 49: 825-827.

56. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey V. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. Correlation with age and cerebrovascular risk factors. Stroke 1986; 17:1084-9.

57. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer. Brain MR: Pathologic Correlation with Gross and Histopathology. Hyperintense White Matter Foci in the Elderly. AJR 1988 151: 559-56.

58. Yetkin FZ, Fischer ME, Papke RA, Haughton VM. Focal Hyperintensities in Cerebral White Matter on MR Images of Asymptomatic Volunteers: Correlation with Social and Medical Histories. AJR 1993; 161: 855-58.

59. Hirano M, Ricci E, Koenigsberger MR. MELAS: an original case and clinical criteria for diagnosis. Neuromuscul Discord 1992; 2: 125-25.

60. Mellies JK, Baumer T, Muller JA, Tournier-Lasserve E, Chabriat H, Knobloch O, et al. SPECT study of a German CADASIL family: a phenotype with migraine and progressive dementia only. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Neurology 1998; 50(6): 1715-21.

61. Fazekas F, Koch M, Schmidt R, Offenbacher H, Payer F, Freidl W, et al. The prevalence of cerebral damage varies with migraine type: a MRI study. *Headache*. 1992; 32:287-291.

62. Committee of the International Headache Society, Classification and Diagnostic Criteria for Headache Disorders, Cranial Neuralgias and Facial Pain. Cephalalgia, 1988 8 (suppl 7): 19-28.

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