09 - 35_Neuropathology

01 - A. Senile plaques

A. Senile plaques

02 - B. Neurofibrillary tangles (NFT)

B. Neurofibrillary tangles (NFT)

1. Alzheimer’s Dementia (AD)

Gross changes include diffuse atrophy, flattened cortical sulci and enlarged cerebral ventricles. Histological changes include neuronal loss (particularly in the cortex and the hippocampus), synaptic loss, granulovascular degeneration (small vacuoles with central granules, in the cytoplasm of neurons especially in the temporal lobes), senile plaques, neurofibrillary tangles and Hirano bodies. Astrocytic gliosis and microglial activation are also noted in some cases. A. Senile plaques Plaques are insoluble amyloid peptide deposits. The peptide involved is called Aß (beta A4) peptide. Amyloids are fibrils of multimeric chains of peptides deposited extracellularly. They have a beta pleated sheet confirmation. Aß is cleaved from a larger transmembrane protein—amyloid-ß precursor protein—by the action of ßand -secretases and its formation is prevented by the action of -secretase. Plaques vary in appearance, and two main subtypes are recognised. Neuritic plaques: o They contain Aß in the form of amyloid fibrils, among which are irregularly swollen dystrophic neurites (degenerated neuronal processes). o The neurites are well visualised with silver stains; they may be seen as an eosinophilic mass on haematoxylin & eosin stains. o Neuritic plaques may contain a dense central core of amyloid. o Microglia and astrocyte processes are present towards the periphery of neuritic plaques. o Seen in Down syndrome and, to some extent, in normal aging as well. o Amyloid sensitive stain Congo red, under polarized light, demonstrates the "apple green" birefringence of the stained tissue with neuritic plaques, due to the presence of beta-pleated sheets. Diffuse plaques: o They consist largely of non-fibrillar extracellular Aß. o They are not related to the degree of cognitive decline o Diffuse plaques contain the same peptides as those responsible for amyloid formation in the neuritic plaques. However, these peptides are not polymerized to form fibrils and lack beta-sheet configuration o Only neuritic plaques are counted in neuropathological tests. B. Neurofibrillary tangles (NFT) NFT are composed of cytoskeletal elements, primarily abnormally phosphorylated tau protein. AD is one of the several degenerative tauopathies. Tau is a peptide required for microtubule assembly. Microtubules are essential to transport of materials down the axons.

03 - C. Hirano bodies

C. Hirano bodies

04 - Neuropathological correlate of cognitive decl

Neuropathological correlate of cognitive decline

© SPMM Course Beta A4 peptide interacts with cholinergic receptors and this interaction stimulates the abnormal phosphorylation of tau. The hyperphosphorylated tau is a major constituent of the tangle. It is also present in the degenerated neurites. Hence both tangles and neuritic plaques can be identified by staining with antibody to the abnormal tau. Apart from Alzheimer's, NFT occur in several disorders including Down syndrome, dementia pugilistica (punch-drunk syndrome), Parkinson-dementia complex of Guam, Hallervorden-Spatz disease, and the normal elderly. Most tangles are faintly basophilic. Tau immunostaining and silver impregnation can be used to improve the chances of light microscopic detection. Tangles are mostly intraneuronal, though upon neuronal degenration, they may appear extracellularly, thus losing their basophilia. According to Love (2005), "the earliest pattern of involvement is usually not associated with clinical symptoms: tangles and neuropil threads are restricted to parts of the entorhinal cortex and the CA1 field of the hippocampus. As dementia develops, tangles and neuropil threads accumulate in increasing density in other parts of the hippocampus and medial temporal neocortex, and then in other cortical regions and in subcortical grey matter structures such as the hypothalamus and thalamus". A staging scheme devised by Braak and Braak (1995) is often employed to describe the extent of tangle related abnormalities (distribution from entorhinal cortex to isocortex) in AD and correlates well with the severity of dementia. Stages V-VI operationally define AD. C. Hirano bodies These are rod-shaped eosinophilic bodies in the cytoplasm of neurons. Hirano bodies are seen in the extracellular space when the neuron dies. Hirano bodies are intracellular aggregates of actin and actin-associated proteins They are frequently seen in hippocampal pyramidal cells Neuropathological correlate of cognitive decline The number and distribution of tangles increases as cognitive decline increases. When both neuritic plaques and tangles are present, the presence of even a few tangles in a single field in the neocortex suggests a significant cognitive decline. There is also an association between the numbers of neuritic plaques and the degree of cognitive decline. However, this is less apparent than the relationship between CEREBRAL AMYLOID ANGIOPATHY (CAA) CAA is the accumulation of Aß in the walls of blood vessels (particularly arteries and arterioles) in the cerebral cortex and overlying leptomeninges.

This affects about 30% of normal elderly people but over 90% of patients with AD, in whom the angiopathy tends also to be much more severe.

CAA is an important cause of strokes in the elderly. Most of these are haemorrhagic; CAA is confined to superficial cerebral blood vessels, rupture of the amyloid laden blood vessels usually causes relatively superficial, lobar haemorrhages that may extend into the subarachnoid space.

05 - Hippocampal pathology

Hippocampal pathology

© SPMM Course tangles and cognitive decline. The best neuropathological correlate of decline is the number of synapses. The marker for synapses has been antibody to synaptophysin, a protein found in the presynaptic endings. Hippocampal pathology The specific cellular pattern of neuronal loss is noted in the subiculum of the hippocampal formation and layers II and IV of the entorhinal cortex. The affected cells connect hippocampal formation with the association cortices, basal forebrain, thalamus, and hypothalamus, structures crucial to memory. This pattern of neuronal loss isolates the hippocampal formation from its input and output, contributing to the memory disorder in Alzheimer patients

Binswanger's disease This is also known as subcortical vascular dementia or subcortical arteriosclerotic encephalopathy Characterized by the presence of many small infarctions of the white matter that spares the cortical regions Often coexists with AD-type changes

06 - 2. Lewy Body Dementia (DLB)

2. Lewy Body Dementia (DLB)

 Lewy bodies are weakly eosinophilic, spherical, cytoplasmic inclusions. In Parkinson’s disease they are confined to substantia nigra; in DLB they are also present in many areas of the cerebrum including the temporal lobe, the cingulate gyrus and the frontal lobes. They may also be found in the dorsal motor nucleus of the vagus. Cortical Lewy bodies are less conspicuous, less eosinophilic and lack clear halo compared to those in the substantia nigra. Cortical Lewy bodies take up a homogeneous eosinophilic staining in the cytoplasm, along with a peripheral displacement of the nucleus. There is no simple correlation between number of Lewy bodies and cognitive decline. Antibody to protease ubiquitin can be used to identify Lewy bodies. Lewy bodies--in Parkinson's disease and DLB contain accumulations of alpha-synuclein. Staining with alpha-synuclein antibodies is an excellent tool for detecting both Lewy bodies. DLB is one of the various degenerative synucleopathies. Alpha-synuclein accelerates reuptake of dopamine in neurons, and this dopamine overload might be toxic. A high proportion of patients with DLB/PDD (about 75%) also have AD-type neuropathological abnormalities. Here the plaque/tangle burden associated with dementia is less than that seen in Alzheimer's disease. Lewy neurites—these are nerve cell processes that contain aggregates of -synuclein. These abnormal structures can occur in both DLB/dementia of Parkinson’s disease and idiopathic Parkinson’s disease and are most numerous in the CA2/3 region of the hippocampus and in the substantia nigra. Some patients with DLB show microvacuolation of the cerebral cortex, predominantly in the medial temporal regions. This can mimic a prion disease.

Tauopathies (tau deposits)

Tauopathies (tau deposits)

•Alzheimer’s dementia •Pick’s disease •Progressive supranuclear palsy •Corticobasal degenerations •Frontotemporal dementia with parkinsonism (FTDP17) Synucleopathies (alpha synuclein deposits) Synucleopathies (alpha synuclein deposits) •Parkinson’s •DLB •Multisystem

atrophy

07 - 3. Frontotemporal Dementia (FTD)

3. Frontotemporal Dementia (FTD)

08 - Frontal lobe degeneration type

Frontal lobe degeneration type

09 - Motor neurone disease (MND) type

Motor neurone disease (MND) type

FTD is associated with three types of underlying pathology: Frontal lobe degeneration type Most common type Spongiform degeneration or microvacuolation of the superficial neuropil is seen chiefly in layers III and V of the cortex. Loss of large cortical nerve cells with minimal gliosis Pick’s type Pick's disease is characterized by a preponderance of atrophy in the frontotemporal regions. These regions also have a loss of large cortical nerve cells, abundant gliosis, and neuronal Pick's bodies, which are masses of cytoskeletal elements. Abnormal swollen oval-shaped neuronal cells with loss of Nissl’s substance and peripherally displaced nucleus are called Pick cells Pick's bodies are seen in some postmortem specimens but are not necessary for the diagnosis. These are argentophilic, tau and ubiquitin reactive filamentous inclusions. Hirano bodies may also be seen albeit with a lesser frequency than in Alzheimer’s. Motor neurone disease (MND) type Cerebral atrophy is less marked; limbic areas are largely preserved Loss of large cortical nerve cells, microvacuolation, and mild gliosis. Ubiquitinated but not tau-immunoreactive inclusions are present within the frontal cortex and hippocampus MND pathology is also seen in anterior horn cells.

HUNTINGTON’S DEMENTIA

Pathologically there is severe loss of small neurons in the caudate and putamen with subsequent astrocytosis.

Characteristic protein deposits form nuclear inclusions in neurons of HD patients.

With the loss of cells, the head of the caudate becomes shrunken and there is "ex vacuo" dilatation of the anterior horns of the lateral ventricles.

10 - 4. Creutzfeldt Jakob Disease (CJD)

4. Creutzfeldt-Jakob Disease (CJD)

 Three forms exist: sporadic (most common), familial and variant CJD (vCJD - related to bovine spongiform encephalopathy). There are no characteristic gross pathologic features of CJD because of the typical short course of the disease. Persons living beyond 6 months to a year may have some degree of generalized cerebral atrophy. Microscopically CJD shows a spongiform encephalopathy secondary to neuropil vacuolisation. Many round to oval vacuoles are seen in the neuropil of cortical gray matter - vacuoles may be single or multiloculated. The vacuoles may coalesce to microcysts. Most cases of CJD also demonstrate neuronal loss and gliosis. Prion protein (PrPc) is a normal neuronal cell surface protein encoded by a gene on chromosome 20. In CJD, this is converted via a conformational change to an abnormal form designated as PrPSc. This abnormal form is protease-resistant and can accumulate in the central nervous system of affected persons. This accumulation triggers further conversion of normal PrPc to PrPSc and accounts for the degenerative changes in the cerebral cortex. The PrP can be identified in tissues with immunoperoxidase staining. These abnormal PrPSc can be transmitted from one person with spongiform encephalopathy to another person via pituitary extracts, corneal transplants, dural grafts, and contaminated electrodes from neurosurgical procedures. In variant CJD, there is a marked accumulation of the prion protein, and the plaques are florid. An abnormal protein called 14-3-3 can be found in the CSF by immunoassay, but this protein is nonspecific and may be found in association with viral encephalitis and stroke. It is less frequent in variant CJD. In familial cases of CJD, the typical EEG changes are often lacking, and the 14-3-3 proteins are absent in CSF in more than 50% of cases. The presence of particular polymorphisms at codon 129 of PrP may have an influence on susceptibility to disease. The amino acids methionine (M) or valine (V) may be present at this locus. In 37% of healthy persons, both inherited PrP genes code for methionine (M/M), and 50% have M/V. In contrast, 73% of persons with sporadic CJD have the M/M phenotype, and 100% of persons with variant CJD have this phenotype. MRI is the most useful supportive diagnostic test in variant CJD. A characteristic abnormality seen in the posterior thalamic region (pulvinar sign) is highly sensitive and specific for variant CJD. The pulvinar sign has been found in more than 90% of pathologically proven vCJD cases. FLAIR sequences of MRI are most likely to

show the abnormality.

© SPMM Course Feature Classic CJD Variant CJD Age Elderly 7th or 8th decade of life Adults in 3rd/4th decade of life Course Shorter course (5 months) More prolonged (1 year) Symptoms Early neurological signs and dementia Early psychiatric/behavioural signs with delayed neurological features EEG Triphasic sharp waves often seen Triphasic waves are rare, and changes are often nonspecific MRI Pulvinar sign is not seen Pulvinar sign is present Biopsy Only a few plaques noted Large number of plaques Tonsils Prion protein cannot be isolated from lymphoid tissue Tonsillar tissue carries prion agent

11 - 5. HIV associated pathology

5. HIV associated pathology

12 - CNS entry

CNS entry

13 - Mechanism of neuropathogenesis

Mechanism of neuropathogenesis

CNS entry The major HIV-1 receptors are CD4 and CD8; various chemokine receptors e.g. CXCR4 and CCR5 are considered as HIV-1 co-receptors. CD4+ helper T lymphocytes are the major routes of multiplication and entry, apart from monocytes. Infected CD4+ T cells and monocytes, which circulate in the blood, are the potential source of CNS infection. The strains of HIV, which are isolated from the brain, have the characteristic of infecting macrophages rather than lymphocytes. Macrophage-tropism is related to a mutation in a specific region of gp120, the external glycoprotein of the virus. In the late stages of the infection, active replication of the virus generates more of these mutants and the compromised immune system permits the escape of these mutants, leading to predominance of macrophage-trophic strains. In order to enter the brain, HIV-1 must cross the BBB using mechanisms that remain unclear. The generally accepted model is the "Trojan Horse hypothesis". HIV enters the CNS as a passenger in cells trafficking to the brain via CD4 T cells or monocytes. Virus accumulation in perivascular regions has been demonstrated as a proof for the above model. An alternative hypothesis of HIV-1 neuro-invasion proposes the entry of free HIV-1 by migration between or, transcytosis of endothelial cells. The mechanism of endothelial infection remains a controversial issue – as CD4 expression in endothelial cells is unclear. Theoretically all the main cell types of the CNS, astrocytes, oligodendrocytes, neurons, perivascular macrophage and microglia, can be infected by HIV-1 since they possess the receptors and/or coreceptors for HIV-1 entry, but only the latter two are the most commonly infected cells by HIV-1. Most studies have indicated an absence of in vivo infection in neurons - It is unclear whether detection of infected neurons is complicated by the loss of the infected neuronal populations. Mechanism of neuropathogenesis Two components of this mechanism are:

1. The direct effect of the HIV-1 infection
2. The indirect consequence of infection comprising the secretion of cytokines and neurotoxins. The infected macrophages and microglia participate actively in the neurodegeneration by: 1) shedding viral proteins and 2) releasing significant amount of

cytokines and neurotoxins into the CNS. 3) Tat and TNF-α contribute to the disruption of the blood-brain barrier, which in turn become more permeable to infected monocytes and cytokines present in the periphery. The secreted pro-inflammatory cytokines activate microglia and astrocytes, which in turn secrete neurotoxins. In addition, the alteration of astrocyte function results in an increase in the level of neurotoxicity in the brain. Neuronal injury via apoptosis is currently believed to be produced by toxic products released directly by HIV-infected macrophages and microglia or by activated astrocytes. Some of these factors have been identified: they include the platelet activating factor, quinolinic acid, nitric oxide, and some

14 - Biopsy findings

Biopsy findings

© SPMM Course metabolites of arachidonic acid, which are neurotoxic, and tumour necrosis factor, which is toxic for oligodendrocytes and can cause demyelination.

Biopsy findings The following can be seen in the biopsy of an HIV infected brain tissue

1. Infiltration of macrophages into the CNS
2. Formation of microglial nodules
3. Multinucleated giant cells from virus-induced fusion of microglia and/or macrophages in central white and deep gray matter;
4. Astrocyte activation and damage;
5. Neuronal loss particularly in hippocampus, basal ganglia and caudate nucleus.
6. A variable degree of white matter pathology with myelin damage
7. Accumulation of lipid macrophages in extreme cases Most common psychiatric presentation in AIDS is HIVrelated dementia, followed by depression. Psychosis is seen only in 10% of HIV-infected individuals.

VIRAL LOAD The current method used to predict stage of disease, to monitor disease progression, and to formulate treatment strategies is to determine viral load (actual number of viral particles found in a cubic millimeter of blood).

HIV-1 can also be detected in the cerebral spinal fluid (CSF). But CSF viral load is not established as an accurate indicator of CNS disease related to HIV.

15 - 6. Schizophrenia

6. Schizophrenia

16 - Gross changes

Gross changes

17 - Histological changes

Histological changes

Gross changes A decrease in brain weight, brain length and volume of the cerebral hemispheres enlargement of the lateral ventricles (especially temporal horns) Reduced tissue volume in the thalamus, in temporolimbic structures including hippocampus, amygdala, parahippocampal gyrus. White-matter reductions in parahippocampal gyrus or hippocampus An increased incidence of a cavum septi pellucidi is noted. Basal ganglia volume reduction was noted especially in preneuroleptic era, in the catatonic subgroup. Enlargement of basal ganglia is now more common in schizophrenia as a consequence of treatment with classical neuroleptics, which can be reversed by the use of atypical substances. Schizophrenia-like psychosis is commoner in temporal lobe epilepsy when the focus is in the left hemisphere. The planum temporale, the posterior superior surface of the superior temporal gyrus, is a highly lateralized brain structure involved with language. In schizophrenic patients, a consistent reversal of the normal left-larger-than- right asymmetry of planum temporale surface area is noted. Heschl's gyrus (primary auditory cortex) showed no differences between the left and right sides.

Histological changes No evidence for astrogliosis in schizophrenia Reduced cell numbers or cell size has been described especially affecting neurons in the hippocampus and DLPFC. Increase in neuronal density, which may relate to the observed decrease in neuronal size (with decreased dendritic arborization and a decreased neuropil compartment) has been reported. Subtle cytoarchitectural anomalies were described in the hippocampal formation, frontal cortex, e.g. a significant cellular disarray in the CA3–CA4 interface Synaptic studies in the hippocampus and DLPFC in schizophrenia show decrements in presynaptic markers. These changes may reflect a reduction in the number of synaptic contacts formed and received in these areas and supports the hypothesis of excessive synaptic pruning in schizophrenia. Glutamatergic synapses may be especially vulnerable in the hippocampus and perhaps the DLPFC, with predominantly GABAergic involvement in the cingulate gyrus. Antipsychotics alter synaptic and neuronal morphology, particularly in the caudate–putamen and may increase glial density in the prefrontal cortex.

18 - 7. Mood disorders

7. Mood disorders

19 - 8. Alcoholic brain damage

8. Alcoholic brain damage

20 - 9. Autism

9. Autism

© SPMM Course 7. Mood disorders A strong association between mood disorder and the number and severity of focal signal hyperintensities on T2-weighted images has been established. These white matter hyperintensities (WMH) occur particularly in the deep subcortical white matter and to a lesser extent in the basal ganglia and periventricular tissue. They are seen in excess in both bipolar and unipolar mood disorder, with an odds ratio of 3 to 7 when compared to healthy controls. In major depression, WMH are particularly common in elderly subjects, where they are linked to risk factors for, and the presence of, vascular disease. This finding is consistent with a robust epidemiological association between the two conditions. WMH confer a poor prognosis in major depression and bipolar disorder. Lithium treatment increases cortical grey matter volume suggesting that lithium is neurotrophic. Lithium may also enhance neurogenesis and inhibit apoptosis Antidepressants may affect neuronal morphology. These agents help regenerate monoaminergic axons, promote hippocampal neurogenesis and prevent the loss of dendritic spines in animal models.

8. Alcoholic brain damage Wernicke's encephalopathy is characterized by degenerative changes including gliosis and small hemorrhages in structures surrounding the third ventricle and aqueduct (i.e. the mamillary bodies, hypothalamus, mediodorsal thalamic nucleus, colliculi, and midbrain tegmentum), as well as cerebellar atrophy. Brain shrinkage can be found in uncomplicated alcoholism, which can largely be accounted for by the loss of white matter. Some of this damage appears to be reversible. Alcohol-related neuronal loss has been documented in specific regions of the cerebral cortex (superior frontal association cortex), the hypothalamus (supraoptic and paraventricular nuclei), and cerebellum.
9. Autism Hypoplasia of cerebellar vermis and to some extent the cerebellar hemispheres is documented. Purkinje cell count in the cerebellum is significantly lower. Inconsistent changes noted in the neocortex. Some suggest increased cortical volume, probably related to reduced pruning.

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and causes. Retrovirology, 3(1), 28.