Alzheimer's Disease

Histomorphological Classification of Disease...

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Alzheimer Disease

Started by C_Duyckaerts, Jan 06 2003 05:15 PM

C_Duyckaerts

Posted 06 January 2003 - 05:15 PM

The diagnosis of Alzheimer disease is clinico-pathological. Clinical information allows the diagnosis of dementia; pathological examination determines with which probability the cognitive deficit is related to Alzheimer lesions.

Alzheimer lesions without dementia may be related to pre-clinical Alzheimer disease. The possibility that they are "normal" at a certain age (due to so-called "physiological aging") has been debated.

There is presently no way to determine if Alzheimer lesions may be observed in the absence of Alzheimer disease.

Immunohistochemistry is presently the most specific way of identifying Alzheimer lesions.

Alzheimer lesions may be graded (which lesions are observed in a specific sample?) and staged (where are the lesions located in the brain?).

The lesions :
The main lesions may be identified by immunohistochemistry, using antibodies against tau protein (tau pathology) or Abeta peptide (Abeta pathology).

1. Tau pathology
The accumulation of tau protein takes place in different subcellular compartments of the neurons. According to this localization, one may distinguish:
Neurofibrillary tangles:
Tau protein may accumulate in the cell body of the neuron as fibrillary structures, which, at electron microscopy, are made of paired helical filaments. The accumulation of tau protein in the cytoplasm of the neuron may not appear fibrillar. It is then called a "pre-tangle".
Neuropil threads:
Tau protein may accumulate in the processes of the neurons. At electron microscopy, this accumulation also corresponds to paired helical filaments
Corona of the senile plaque:
Tau protein may accumulate in the axons, which surround the amyloid core of the senile plaque. Core and corona make a senile plaque.

2. A-beta pathology
The accumulation of A-beta peptide is mainly extracellular and is observed mainly in the cerebral cortex.
--When the deposit is large, ill-limited and weakly immunolabeled, it is called diffuse.
--When the deposit is small, round, strongly labeled, it is called focal.
--When the deposit is stained either with Congo red or thioflavin S, the adjective "amyloid" is appropriate.

Senile plaque
A senile plaque (synonym: neuritic plaque) is made of focal A-beta deposit (the core) and of a corona of tau positive processes.

The grade of lesions:

Different methods of grading are possible, have been suggested and should be discussed : the counting of the senile plaques or of the neurofibrillary tangles present in one area is one of them.
The grading of the lesions may also be based on the way they commonly associate. This is a proposal to be discussed:

In the entorhinal / hippocampal regions
Grade 1 : Tau pathology is present in the absence of a-beta deposits
Grade 2: Tau pathology is associated with diffuse a-beta deposits
Grade 3: Tau pathology is associated with focal a-beta deposits
In the isocortex
Grade 1: diffuse and focal deposits of A-beta peptide are seen.
Grade 2: focal deposits are Congo red positive. Macrophages are seen in close contact with the amyloid deposits.
Grade 3: focal deposits are surrounded by tau positive neurites
Grade 4: neurofibrillary tangles are associated with the previous lesions.

The stage of the disease:
The stage of the disease depends on the topography of the neurofibrillary pathology.
It is first restricted to the entorhinal cortex (entorhinal stage). It later involves the hippocampus (hippocampal stage). Finally, it also affect the isocortex (isocortical stage), first the associative areas ("associative areas" substage) and later the primary cortices ("primary areas" substage).

Diagnosis
Pure Alzheimer disease is certain when dementia is associated with an isocortical stage in the absence of other lesions (such as Lewy bodies or infarcts - to be discussed in later versions).

The probability that Alzheimer disease explains a specific cognitive deficit is high when neurofibrillary pathology involves cortical areas supposed to be involved in the cognitive process that is defective.

There is a debate concerning the possibility of making the diagnosis of Alzheimer disease when only amyloid deposits or neurofibrillary pathology are present.

Admin

Posted 12 January 2003 - 10:42 AM

There are several issues which are raised by the definitions proposed for Alzheimer's disease. To keep discussion focused it is probably best to start several new topics that debate each area.

One topic I would like to start relates to immunohistochemistry as follows:

Does this definition imply that immunohistochemistry is the only way to make a pathological diagnosis of Alzheimer's disease? If not, how is the interpretation of other stains brought into the definition?

C_Duyckaerts

Posted 01 February 2003 - 04:18 PM

What would be the purpose of keeping silver stain in the definition of the disease ? When a true diagnostic problem arises, Abeta and tau immunohistochemistry are indispensable. Silver stains are either use because they have been routinely used or for special purposes (as in very thick sections as Heiko Braak did). I do not believe they should be included in the definition of the disease.

I fully agree with the drop of "secondarily" in the entorhinal/hippocampal grades.

Grade 4 : I meant grade 3 lesions are associated with neurofibrillary tangles.

I corrected that in the definition.

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Grading Of Lesions In Alzheimer's Disease

Started by Jim Lowe, Jan 12 2003 11:13 AM

Jim Lowe

Posted 12 January 2003 - 11:13 AM

In the definition posted for Alzheimer's disease, the following grading system has been proposed:

In the entorhinal / hippocampal regions:

Grade 1: Tau pathology is present in the absence of a-beta deposits

Grade 2: Tau pathology is associated with diffuse a-beta deposits

Grade 3: Tau pathology is associated with focal a-beta deposits

[Note: it may be premature to state a-beta deposits are SECONDARILY associated with tau, as stated in the origional proposal]

In the isocortex:

Grade 1: diffuse and focal deposits of a-beta peptide are present.

Grade 2: focal deposits of a-beta peptide are also Congo red positive. Macrophages are seen in close contact with the amyloid deposits.

Grade 3: focal deposits are surrounded by tau-positive neurites

Grade 4: neurofibrillary tangles are present.

Comments:
1. There is a possibility that some diseases with tau pathology alone may not be Alzheimer's disease. Should the definitions proposed acknowledge and anticipate this. For example 'tangle-only' dementia.

2. In the isocortex, it is possible to have Grade 4 disease in the absence of a-beta deposits: was this intentional? Should AD be defined as the combination between a-beta pathology and tau pathology?

3. The definition for isocortical stage above 2 would imply specific detection of macrophages as part of the grading process. I would suggest that this adds too much to the burden unless there is strong evidence that this is a pivotal and defining feature that separates cases.

4. Should vascular a-beta deposition be included in this grading definition?

5. Should neuronal loss be included in a grading definition? I feel that if we are proposing gradings they will eventually be used in the context of trying to relate the response of patients to treatment to their pathology. Neuronal loss is an important aspect of Alzheimer's disease.

C_Duyckaerts

Posted 01 February 2003 - 04:33 PM

Should vascular a-beta deposition be included ?

Possibly, but who knows when vascular deposition occur ?

Neuronal loss in the grading system ?

If neuronal loss is to be evaluated, then the volume of the sample has to be measured as well as the volume of the cortex. Then, the di-sector method should be used. I feel it is presently difficult to do regularly, unless one accepts to resort to a simple evaluation of the number of neuronal profiles per mm2, a biased measure as stereologists will rapidly tell.

Jellinger

Posted 17 November 2003 - 08:55 AM

The question, whether A-beta vascular deposition should be included in the proposed grading definition, one should consider the results of recent studies showing that general CAA (congophilic angiopathy) did neither correlate with the presence of dementia nor with high grade of AD pathology (Braak stages), while capillary CAA ("dyshoric angiopathy") grading highly correlated with CERAD, Braak and NIA-R criteria of AD. Presence/Severity of CAA and CapCAA showed low correlations.
These data and comparing A-beta-40 and –42 immunohistochemistry suggest different pathomechanisms for CAA (mainly A-beta-40 positive) and both CapCAA and amyloid plaques (mainly A-beta-42 positive). Hence, only CapCAA and not CAA should/could be included in the grading system of AD. A certain number of demented aged subjects show severe CAA and low grade AD-pathology which should be taken into consideration. (see J.Attems, K.A.Jellinger, 105th Meeting BNS, London, 7.-9.Jan. 2004, Acta Neuropathol, in press).

Graeber

Posted 23 October 2004 - 04:24 PM

After more than 100 years of silver "staining" (Bielschowsky, 1902), AD research should tremendously benefit from consensus on the application of more precise, i.e. molecularly defined tools such as monoclonal antibodies directed against beta-amyloid and tau which are now widely (commercially) available. There is little justification in my view for the continued use of silver methods especially in a research setting; their time is up. Existing silver-based hypotheses should be translated into molecular concepts and tested accordingly.
Examples
Antibodies to Beta Amyloid Proteins (http://www.alzforum.org/res/com/ant/Beta-Amyloid/BETAAM-tableC.html)
Antibodies to Tau-related Proteins (http://www.alzforum.org/res/com/ant/tau/TAU-tableC.html)

Gentleman

Posted 10 August 2005 - 04:50 PM

Having applied this system of grading Alzheimer pathology for a while now I have a couple of comments:

The first is with regard to nomenclature. The senile (neuritic) plaque has been succinctly defined as a focal A-beta deposit surrounded by a corona of tau positive neurites and is relatively easy to identify. However there are focal A-beta deposits that appear identical to those seen in the senile plaques except that they do not have an associated tau positive corona (presumably the same as those described under the Grade 2 isocortical definition). I've been calling these cored plaques to differentiate them on the one hand from neuritic plaques and on the other hand from less compacted focal deposits. Is this a useful term or is the term "focal deposit" reserved specifically for compacted cores and everything else in the spectrum of A-beta staining should be referred to as diffuse?

The second point concerns the Grade 2 isocortical definition. The point has already been raised that macrophage detection is probably not essential in terms of a routine diagnostic report. In the same vein is it still necessary to carry out a Congo Red stain? What does it add in terms of what is now an immunocytochemical diagnosis?

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Is IHC Now Essential For AD Diagnosis?

Started by Jim Lowe, Jan 12 2003 10:54 AM

Jim Lowe

Posted 12 January 2003 - 10:54 AM

It would seem that this definition now implies that immunohistochemistry is the only way to make a pathological diagnosis of Alzheimer's disease. This has major implications but as it may be appropriate should be debated and evidence supplied as to why we might want to move in this direction.

I would suggest that *for diagnosis* certain silver stains are as good as IHC for defining deposits of a-beta: for example those methods related to the original methenamine silver techniques.

I am not certain that one can reliably distinguish between fibrillar and non-fibrillar forms of intraneuronal tau by light microscopy and IHC. Does this matter? Are tangle and pre-tangle accumulations of tau protein to be given equal weighting in diagnosis of AD?

C_Duyckaerts

Posted 01 February 2003 - 04:43 PM

Silver stains cannot be used in a definition any more since their target ("antigen") is not precisely known. This is why, personally, I would like to include tau and abeta in the definition of the disease and that means IHC. This does not imply, I think, that silver stains are forbidden for diagnostic purposes. Do you think it should be stated that for diagnostic purposes, silver stains may be used etc....? Is it necessary to speak latin to understand italian ?

Concerning the fibrillar aspect of the pathology, it might suggest that electron microscopy is essential. I dont know. It could be another layer of the diagnosis. (We could also add a biochemical layer mentioning that tau is 3- and 4- R).

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Is Immunochemistry Essential In Diagnosis?

Started by Jim Lowe, Jan 12 2003 11:23 AM

Poll: Is Immunochemistry Essential In Diagnosis? (8 member(s) have cast votes)

Is Immunochemistry Essential In Diagnosis?

Yes: The pathological definition of Alzheimer's disease should in future be based on immunohistochemical staining for a-beta and tau. Immunohistochemistry should be made ESSENTIAL for pathological diagnosis. (3 votes [60.00%])

No: The pathological definition of Alzheimer's disease should in future allow for other staining methods. Immunohistochemistry should be OPTIONAL for pathological diagnosis. (2 votes [40.00%])

Jim Lowe

Posted 12 January 2003 - 11:23 AM

Please vote on the proposal that, for the future, a pathological definition of Alzheimer's disease will only be based on immunohistochemical assessment for a-beta and tau protein.

NOTE: This is the first poll/vote on ICDNS. Users may not be familiar with how they work. To vote you MUST be registered and logged in. If you are using this as GUEST you will not see the voting option - just the results.

The poll/voting only allows for one vote per person. To vote, choose the response that you agree with by clicking in the appropriate radio button. Then click the "Vote" button.

If you click on "View Poll - Null vote" you will not be allowed to voice your opinion in the future on this topic. Only click on this button if you do NOT intend to voice your opinion.

Graeber

Posted 12 January 2003 - 09:27 PM

It would seem important to obtain consensus on

i) What are the most widely accepted staining methods at the moment, i.e. what does the current baseline look like?

ii) Which method of quantification (for the two main types of lesions) is to be employed, if at all?

This will influence the decision on whether IHC becomes mandatory. After all, antibody stainings need to be standardised and this can be quite complex (general, non-commercial? availability of the antibody, monoclonal or polyclonal etc.).

In practice, it may not be possible yet to implement an IHC-based diagnosis of AD although a widely exercised molecular characterisation of the extracellular and intracellular protein "deposits" would be attractive.

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