Intravenous IGs

Intravenous immunoglobulins: a treatment for Alzheimer's disease?

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A novel therapeutic option for Alzheimer's disease

Aβ-peptide is generally considered to play a central role in the pathogenesis of Alzheimer's disease (AD). The peptide is cleaved from amyloid precursor protein (APP) by secretases and is a key component of the amyloid plaques. Amyloid plaques may also contain other proteins such as serum amyloid P component (SAP), activated complement proteins, clusterin, and α1-antichymotrypsin. Observations in mice carrying the human APP transgene support the importance of Aβ-peptide as a driving force for intracerebral amyloid deposits in AD. The mechanisms leading to neurotoxicity and neurodegeneration induced by Aβ-peptide are not yet clear. According to one scenario deposits of Aβ-fibrils, together with associated proteins, are toxic for neurones—either directly or indirectly—by recruitment and stimulation of microglial cells. An alternative scenario claims a major role of Aβ-oligomers as mediators of neurotoxicity.[1] Clearance of intracerebral amyloid deposits is currently one of the therapeutic options under investigation for AD.

Recently it was found that vaccination with Aβ-peptide slowed down the amyloid accumulation in the brains of APP transgenic mice,[2] the effect of which could be reproduced by administration of anti-Aβ antibodies.[3] This has led to clinical studies on the effect of active immunisation of AD patients with Aβ-peptide. Although promising results in some patients were observed, this active immunisation approach was accompanied by severe side effects—in particular, severe meningoencephalitis.

Specific antibodies against Aβ-peptide suitable for treatment in AD patients are not yet available. In this issue (pp 1472), Dodel and coworkers describe the effects of passive immunisation with intravenous immunoglobulins (IG) in five patients with AD.[4] Intravenous IG are prepared from plasma pools of thousands of normal donors, and initially were developed as a substitution therapy for immunodeficient patients. Later, intravenous IG was found to be beneficial in a number of inflammatory or immune disorders including some neurological diseases such as chronic inflammatory demyelinating polyneuropathy and possibly multiple sclerosis.[5] Because healthy individuals have circulating auto-antibodies against Aβ-peptide, intravenous IG contains antibodies against Aβ-peptide as well. For this reason Dodel *et al* evaluated the effect of this drug in patients with AD. Total levels of Aβ-peptide decreased in cerebrospinal fluid (CSF) in the five patients evaluated, whereas levels of the peptide in serum increased. No effect on Aβ1-42 levels were observed. In addition, stabilisation or even a mild improvement in cognitive function was observed in the patients.

These results raise a number of questions. Firstly, the number of patients studied is small and, therefore, as the authors also indicate, larger studies are needed to confirm that this treatment can stabilise or even improve cognitive functions in AD. Secondly, a dose of 0.4 g intravenous IG per kg body weight for three consecutive days every 4 weeks for 6 months was given—a regular dose used in immune disorders. Because the patients were given only one dose it is unclear whether this dose is optimal. Thirdly, the mechanism of action of intravenous IG in AD patients is not clear. The authors postulate that the effects are mediated by antibodies against Aβ-peptide, which indeed are present in intravenous IG. However, if these antibodies would mediate the effect, it is still not clear how they do so. Enhanced clearance of total Aβ-peptide is not supported by the increased levels in serum, which actually are more consistent with decreased clearance—at least in the periphery. On the other hand, the lower CSF levels support enhanced clearance in the cerebral compartment. However, it is puzzling why levels of Aβ1-42 did not change upon intravenous IG treatment because this peptide is considered to be the most pathogenic Aβ-peptide in AD. Therefore, if the beneficial effects of intravenous IG were due to the presence of anti-Aβ antibodies, it would be more likely that they may have been related to a neutralising effect on toxicity of Aβ on neurones. A series of studies in vitro and in vivo on the effects of intravenous IG have shown that it has many other effects on immune and inflammatory reactions that may be relevant for its mode of action in AD. For example, intravenous IG has been shown to interfere with complement deposition onto targets. Indeed, amyloid plaques of AD contain activated complement proteins. Efficient inhibition of complement fixation to targets by intravenous IG occurs at higher doses of intravenous IG (2 g/kg/day) than those administered in the study by Dodel *et al*. Hence, if the complement modulating effect is the mechanism of action in AD, it can be predicted that somewhat higher doses may even lead to better clinical effects. Another intriguing possibility is that intravenous IG may have affected the function of activated microglial cells surrounding the plaques. Animal experiments in rats have clearly shown that intravenous IG can stimulate macrophages and neutrophils via Fc receptors.[6] Therefore, it is comprehensible that the brain microglial cells become stimulated upon intravenous IG administration, leading to enhanced clearance of amyloid deposits. Furthermore, changes in cytokine levels have been repeatedly found in response to intravenous IG administration. Hence, one could also postulate that the effects of intravenous IG in the AD patients described by Dodel *et al* were due to altered cytokine production by microglial cells.

Definite conclusions regarding the use of intravenous IG in AD—with respect to both the clinical effects as well as to the mode of action—cannot be made on the basis of the study by Dodel and coworkers. However, the paper highlights a novel and interesting therapeutic option for AD, which seems worthy to be explored in further studies. In addition, the effects of intravenous IG may need to be studied in the transgenic mouse models for AD to better understand the mechanism of action.

J Neurol Neurosurg Psychiatry
2004;**75**:1374–1375.
doi: 10.1136/jnnp.2004.043141

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Multiple lacunar infarct mechanisms

Are multiple acute small subcortical infarctions caused by embolic mechanisms?

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Multiple lacunar infarct mechanisms

In this issue the paper by Chowdhury *et al* (see page 1416)[1] is an important addition to the list of recent publications that challenge traditional concepts on the mechanisms of acute ischaemic stroke. According to conventional teaching, an acute ischaemic stroke is characterised by infarction confined to a single localised (focal) region of the brain. However, new neuroimaging techniques—in particular diffusion weighted magnetic resonance imaging (dw-MRI)—have modified this view.

In a recent study,[2] scattered lesions in one vascular territory or multiple lesions in multiple vascular territories were actually more common than single lesions. Although dw-MRI is very sensitive in the ultra-early detection of cerebral ischaemia, it should be recognised that the dw-MRI lesions are not equivalent with infarction. Dw-MRI abnormalities may be reversible if the level of ischaemia is mild, or if early reperfusion occurs—for example, by means of thrombolytic therapy. Nevertheless, dw-MRI findings may give clues to underlying pathophysiology.

Scattered or multiple acute ischaemic lesion patterns have been associated with embolism from cardiac or large artery sources,[2] which, in particular, should also be logically plausible if cortical territories are involved. However, in the present series of 10 patients with multiple infarcts mainly confined to subcortical regions,[1] an embolic source was found in only one case. Could an embolic source have been over-looked? The possibility cannot be excluded because the patients were not investigated with trans-oesophageal ultrasound (which might have disclosed atherosclerotic aortic arch disease, for example); however, it appears unlikely.

The dw-MRI findings suggested that the subcortical lesions had occurred within several weeks rather than at exactly the same time. Also in this field, concepts have changed: the acute phase of ischaemic stroke is much more dynamic than previously thought. A recent dw-MRI study[3] disclosed early recurrent lesions on neuroimaging in one third of all patients within the first week, while clinical recurrence was evident in only 2%. Accepting that embolism is the unlikely cause in the present series, what other mechanisms may cause a clustering of multifocal cerebral ischaemia? At present, the answer is unknown but systemic factors like blood pressure regulation, haemorheological factors, infection, endothelial dysfunction, and possibly even stress might contribute. The present study underscores current gaps in the knowledge of precipitating causes of acute cerebral ischaemia—an under-investigated topic.

The present study also highlights recent insights that ''silent'' or ''covert'' cerebral infarcts are severalfold more common than ischaemic stroke, i.e. infarcts that present with the acute onset of focal neurological deficits. According to a recent analysis, less than 7% of all cerebrovascular lesions are associated with overt clinical symptoms, i.e. fulfilling the definition of stroke.[4] Covent cerebrovascular lesions are important determinants for cognitive dysfunction, dementia, recurrent stroke, and death.

Recent technological advances have provided us with the tools for research into these issues. Progress in diagnosis and prevention of overt and covert cerebrovascular disease will require an open mind, ready to challenge traditional concepts of cerebrovascular disease.

J Neurol Neurosurg Psychiatry 2004;**75**:1375.
doi: 10.1136/jnnp.2004.046748

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