INvolvement of the vessels and the blood brain barrier in autoimmune diseases leading to dementia

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Systemic autoimmune disorders such as systemic lupus erythematosus (SLE)¹, multiple sclerosis (MS)²,³ and antiphospholipid syndrome (APS)⁴,⁵ are often associated with dementia and the pathogenic mechanisms involved include significant effects on the blood vessels of the brain. These effects include infarcts, disruption of the blood brain barrier (BBB) and penetration of brain reactive antibodies and inflammatory cells⁶-⁹. A prototype for a single systemic autoimmune disease displaying most of these pathogenic mechanisms is the APS. This review will put special emphasis on this syndrome which is defined by the existence of antiphospholipid antibodies (APLAb) and in which much work had been done and which exemplifies the complex issues of systemic coagulation, activation of endothelial cells, penetration of antibodies through the BBB, and specific antibodies which cross reacting with the brain. APS may therefore be considered as a prototypic form of vascular dementia and this theme will be developed in the following discussion.

APS is generally defined by the presence of APLAb together with thromboembolic events or recurrent, mainly vascular mediated, fetal loss. The syndrome may occur as a primary disease or be secondary to other systemic autoimmune diseases such as SLE with which it has a large overlap. There are a number of established mechanisms by which APS may induce recurrent stroke which include an increase in thrombosis, inhibition of fibrinolysis, accelerated atherosclerosis, cardiac valve disease (endocarditis),

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artery dissection and endothelial cell activation. Epidemiologically there is substantial evidence linking APS with recurrent stroke and there have been a number of case reports and case series linking APS with dementia. In addition to clear cases of large and clinically evident strokes there is data to show that APS may lead to dementia by more subtle microvascular disease, white matter changes or by non-ischemic mechanisms which may lead to penetration of the BBB by antibodies which interact directly with brain tissue.

Interestingly, in most of the well-established animal models of APS it is difficult to demonstrate overt cerebral vascular disease even when these are carried out in thrombosis susceptible factor V Leiden transgenic mice. In fact, the animal models have provided evidence for antibody penetration into the brain with specific effects on structure and function (Frauenknecht 2 refs). There are a number of findings supporting the possibility that the autoantibodies specific for APS may be involved both in the disruption of the BBB and directly interact with neurons and glia in human subjects: Firstly there are a number of mechanisms that APLAb may directly disrupt the BBB. These include endothelial cell activation by direct antibody binding, thrombosis with increased thrombin activity activating protease activated receptors and inflammatory changes. Antibodies to blood vessel components including antiphospholipid antibodies are known to cause activation of endothelial cells. Interestingly activation of the coagulation system and specifically thrombin have a very similar effect through the thrombin receptor protease activated receptor (PAR-1). One of the key components of the coagulation system is the fibrinolytic cascade which includes both tissue plasminogen activator (tPA) and plasmin. A central feature of APS is an impairment of the fibrinolytic pathway since the major antigen associated with the syndrome is β2-glycoprotein-I (β2-GPI) which is a major component of a membrane bound complex which mediates the conversion of plasminogen to plasmin by tPA. Furthermore, other components of this complex have been identified as autoantigens in APS, most notably annexin A2. This protein is indeed commonly expressed on endothelial where it forms a tetramer and this tetramer acts as a co-activator of plasminogen. Thus, antibodies to either β2-GPI or annexin A2 may stimulate endothelial cells in a number of various mechanisms leading to disruption of the BBB and allowing components of the blood
to enter the brain and whether these are coagulation factors, cytokines or auto-reactive antibodies, they may impair brain function. Secondly, it is important to note that coagulation factors and their receptors (PARs) are produced in the brain and play an important role in brain function especially in synapses and nodes of Ranvier (Shavit et al, x2). Pathological processes in APS brains may include both increased coagulation factors entering the brain and the effects of antibodies on the activity of coagulation factors in the brain itself.

The pathophysiological processes underlying dementia in APS are directly relevant to therapy and a number of possible approaches have been suggested and studied. In APS the major approach has been to inhibit coagulation by both anticoagulants and antiplatelet agents. This approach is successful in some patients but is not sufficient to prevent brain damage and dementia in others. More active approaches are now being considered including immunosuppression such as plasma exchange, intravenous immunoglobulins and rituximab. The success of these approaches is also limited and a more detailed understanding of the mechanisms and therapeutic targets is crucial to progress in this matter. The epidemiology of APS and especially its relationship to age is well worth noting regarding the possibility that autoimmune diseases cause dementia. In young patients cognitive impairment in the antiphospholipid syndrome is associated with triple positive antibodies (explain) and with systemic involvement such as deep vein thrombosis and recurrent fetal loss. The situation in elderly patients is not yet completely understood. The level of APL antibodies goes up with age and is quite common. However, most of these antibodies are positive only for one antigen, usually cardiolipin, and are of medium titers. Large clinical studies have failed to prove that anticoagulation in these patients is superior to anti-platelet medications. This is in contrast to the accepted though not absolutely proven efficacy of anti-coagulation in younger patients. If proven to be clinically significant the relatively large amounts of elderly patients with APL would represent a very significant therapeutic target and suggest searching for other autoantigens relevant to dementia.