

# Histopathological changes in the human brain following infection with *Neisseria meningitidis*

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## INTRODUCTION

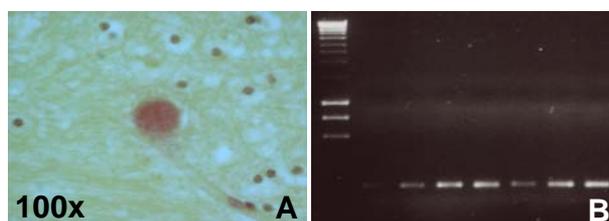
*N. meningitidis* is a leading cause of bacterial meningitis and septicaemia in children and young adults. The lack of understanding of the mechanisms of cerebral injury caused by meningococcal infection is a major impediment to developing new adjunctive therapies. Here, meningococcal invasion and histopathological changes in neuronal tissue were investigated to further define the extent of disease, and to provide the basis for developing effective interventions to reduce mortality and morbidity.

## METHODS and MATERIALS

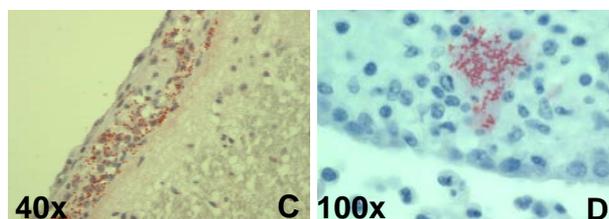
Samples were obtained from 21 children succumbing to bacterial meningitis in Abidjan, Cote d'Ivoire. *N. meningitidis* was identified by Gram staining, PCR of *ctrA* sequences and localization by immunohistochemistry with polyclonal anti-meningococcal sera (Stratech Ltd.). Endothelial cells were stained with an anti-CD31 antibody. Inflammatory responses were detected by immunostaining for neutrophils (neutrophil elastase), macrophages (CD68), activated microglia (anti-lectin *Ricinus communis agglutinin-1*) and astrocytes (glial fibrillary acidic protein). Neuronal and other cell death was detected by TUNEL and active caspase-3 staining. Axonal and cerebral vascular injury was demonstrated by detection of  $\beta$  amyloid-precursor protein (APP) and fibrinogen extravasation, respectively.

## RESULTS

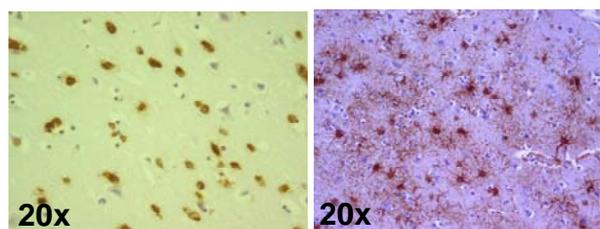
*N. meningitidis* was detected in the brains from 6 of 21 patients by Gram staining (Fig. A, bacterial colonies stained red, size bar, 10  $\mu$ m), PCR (Fig. B, 111 bp PCR products in agarose gel) and immunohistochemistry.



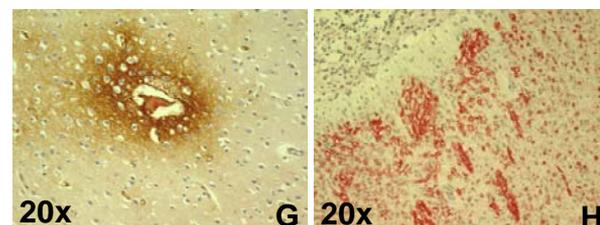
Numerous bacteria were present in the sub-arachnoid space and the ventricles (not shown). Furthermore, bacteria were distributed in the meninges (Fig. C, red staining) and the interstitium of the cortex, cerebellum (Fig. D, red staining), the brain stem, and were present in choroid epithelial and ependymal cells.



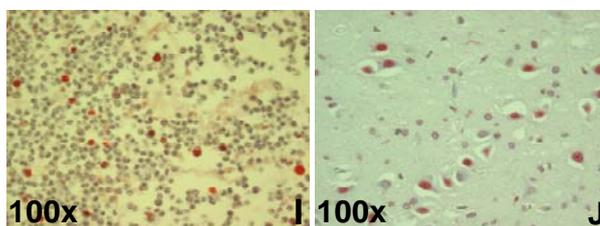
Large numbers of neutrophils were seen in brain parenchyma (Fig. E, brown staining) and ependyma, indicating ventriculitis and encephalitis (not shown). Glial activation (Fig. F, astrocyte activation brown staining) was also widespread.



The loss of integrity of the blood brain barrier (BBB) was demonstrated in all regions by fibrinogen leakage (Fig. G, brown staining). APP accumulated in the axonal network and neuronal bodies throughout brain in all patients (Fig. H, red staining) indicating disruption of axonal transport and function.



Apoptosis and cell death was present affecting infiltrating phagocytic cells (Fig. I, TUNEL staining red), numerous neurones (Fig. J, TUNEL staining red) and glial cells, and some choroid epithelial and ependymal cells (not shown).



## CONCLUSIONS

*N. meningitidis* was present not only in the sub-arachnoid space but also in the parenchymal of the central nervous system, where it elicited a marked inflammatory response, resulting in widespread axonal and BBB disruption, and extensive apoptosis.

Acknowledgements: Dr Y Li is funded by Meningitis Research Foundation