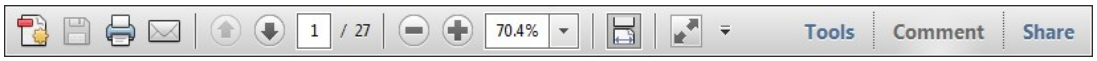
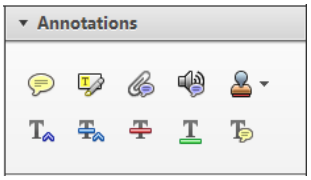
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

WILEY

Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

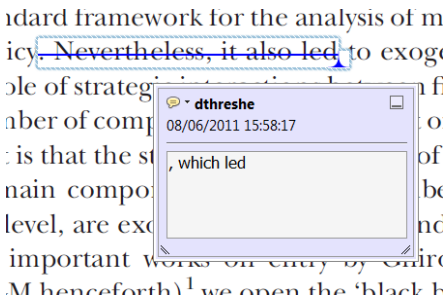


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

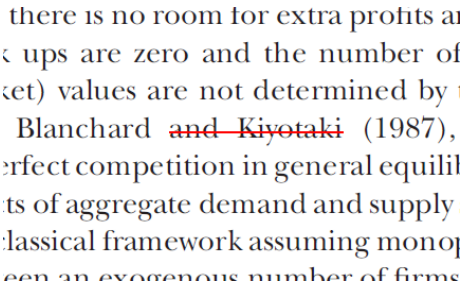


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

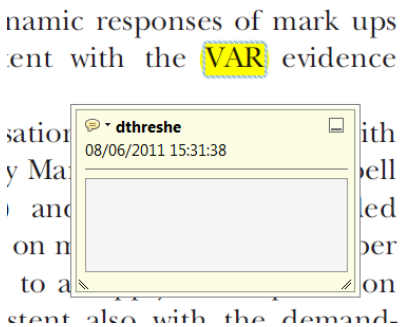


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

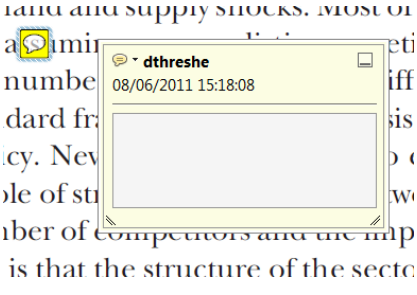


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.

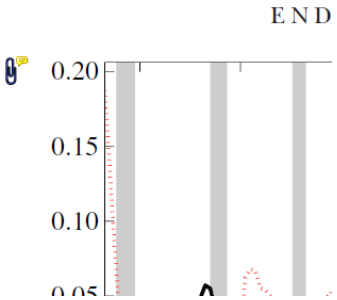


5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate place in the text.

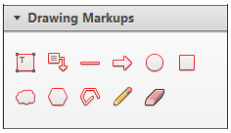
How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.



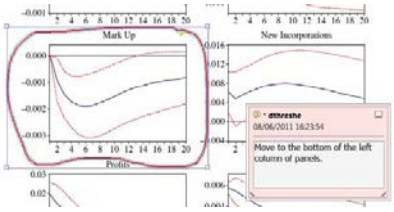
6. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks.



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



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Decoding the association between herpes simplex virus and antibody-mediated encephalitis

MARK A ELLUL[1] | MICHAEL J GRIFFITHS[1,2]

1 Institute of Infection and Global Health, University of Liverpool, Liverpool; **2** Alder Hey Children's NHS Foundation Trust, Liverpool, UK.

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This commentary is on the original articles by Nosadini et al. and Kothur et al. To view this papers visit https://doi.org/10.1111/dmcn.13471.

Most cases of encephalitis are caused by either viral infection or an antibody-mediated process, although in virtually all studies a high proportion of patients have no aetiological diagnosis. Recently, the diagnosis and management of encephalitis has become more complex, with the awareness that herpes simplex virus encephalitis (HSE) can be associated with a secondary anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. There is early evidence of inflammatory mediators being distinct between infective and antibody-mediated encephalitis.[1] However, the number of patients is small, and no studies have examined host responses in anti-NMDAR encephalitis following HSE.

Two complementary studies add to this evolving story. Nosadini et al. review the literature on the association between HSE and anti-NMDAR encephalitis.[2] Kothur et al. extend insight into host inflammatory responses in viral and antibody-mediated encephalitis, including one case of HSE-induced anti-NMDAR encephalitis.[3]

Nosadini et al. succinctly summarize the literature on anti-NMDAR encephalitis associated with HSE in adults and children.[2] Forty-three patients were identified, including a newly reported case. Overall, the secondary anti-NMDAR phase was associated more frequently with movement disorders and less with seizures than the initial infective phase. These features may be useful in clinically distinguishing autoimmune from active viral encephalitis.

The authors also reviewed patients with HSE in whom anti-NMDAR antibodies were detected retrospectively. There is controversy as to whether these antibodies, often of subclasses other than IgG, are driving clinical symptoms and whether these subclasses are truly pathogenic. A number of patients also had HSV detected by PCR in cerebrospinal fluid (CSF) during a clinical episode of anti-NMDAR encephalitis: again the clinical significance of this is uncertain. The review highlights the need for better understanding of these conditions and how they interact.

Kothur et al. measured a panel of CSF chemokines and cytokines in a child with HSE induced anti-NMDAR encephalitis during acute admission and recovery, and compared patterns of abundance with children suffering chronic or relapsing HSE, pure anti-NMDAR encephalitis and controls.[3]

Most of the assayed cyto/chemokines were elevated in acute HSE, while in the post-HSE anti-NMDAR phase there was persistent elevation of a few key mediators. Interestingly, the cyto/chemokine elevation in the HSE/NMDAR case was more florid than in anti-NMDAR encephalitis alone. Most patients with chronic or relapsing HSE showed persistent mediator elevation, suggesting ongoing neuroinflammation, supported by histopathological evidence in one patient. Nevertheless, some patients had a response to immune therapy. This study underlines the potential of examining host responses to gain insight into the role of inflammation during encephalitic illness.

The rapid development of transcriptomic and proteomic approaches offers an opportunity to identify specific patterns of biomarkers involved in infective and antibody-mediated encephalitis. Such techniques are already beginning to provide insight into mechanisms of injury and identify potential adjunctive treatments for HSE.[4]

The most effective treatment for antibody-mediated encephalitis remains unknown. A range of immune therapies are currently used, and management is non-standardized and based on limited evidence.[5] Currently, evaluating treatment response relies on clinical symptoms and antibody levels in serum or CSF. Antibody titres do not reliably predict treatment response,[6] and poor outcome or relapse can occur despite low levels. There is a need for accurate markers of disease activity to enable more personalized immune therapy.

Biological agents (e.g. anti-TNF therapy) are increasingly used to treat extracranial autoimmune disorders. As yet, it is unclear which (if any) biologic will reduce relapse and morbidity in encephalitis. There is a need for well-conducted trials to address the management of these conditions. Host responses in brain inflammation could act as proxy markers of treatment response, or even provide potential therapeutic targets for host-directed therapies. Specific host response patterns that distinguish antibody-mediated from infective encephalitis would guide and rationalize investigation. This would enable clinicians to initiate appropriate treatment more promptly, benefiting patients.

With the analysis of larger, well-defined patient cohorts, further innovative longitudinal studies should aim to characterize host response patterns to enable stratification of patients into aetiological and prognostic categories, including patients with HSE at risk of developing secondary anti-NMDAR encephalitis. Paediatric and adult researchers should pool their clinical resources to gain better understanding and develop new treatments for these devastating conditions.

REFERENCES

1. Michael BD, Griffiths MJ, Granerod J, et al. Characteristic cytokine and chemokine profiles in encephalitis of infectious, immune-mediated, and unknown aetiology. *PLoS ONE* 2016; **11**: e0146288.
2. Nosadini M, Mohammad SS, Corazza F, et al. Herpes simplex virus-induced anti-*N*-methyl-D-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. *Dev Med Child Neurol* 2017. https://doi.org/10.1111/dmcn.
3. Kothur K, Gill D, Wong M, et al. Cerebrospinal fluid cytokine/chemokine profile during acute herpes simplex virus-induced anti-*N*-methyl-D-aspartate encephalitis and in chronic neurological sequelae. *Dev Med Child Neurol* 2017. https://doi.org/10.1111/dmcn.
4. Wnek M, Ressel L, Ricci E, et al. Herpes simplex encephalitis is linked with selective mitochondrial damage; a post-mortem and in vitro study. *Acta Neuropathol* 2016; **132**: 433–51.
5. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother* 2015; **15**: 1391–419.
6. Zandi MS, Paterson RW, Ellul MA, et al. Clinical relevance of serum antibodies to extracellular N-methyl-D-aspartate receptor epitopes. *J Neurol Neurosurg Psychiatry* 2014; **86**: 708–13.

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