

What is impact?



EDITOR'S
CHOICE

Matthew C Kiernan



The word 'impact' is in peril of becoming hackneyed terminology. In modern parlance its meaning appears to have undergone more costume changes than Lady Gaga on a whistle-stop tour! And in the world of medical publishing the definition of 'impact' is nowhere more nebulous than where a ground breaking paper, and a review that merely cites a ground breaking paper, are measured using the same impact criteria.

How then does one judge the impact of a publication, both at the time and thereafter? For instance, in high turnover publications such as daily newspapers, initial impact may be phenomenal, although transitory, from front page scoop, to fish and chips wrapping in the space of a single day. When considering medicine, and particularly medical publications, presumably the desired impact would mean that manuscripts were read, information conveyed and subsequently adopted by the reader, and as a consequence, practice was changed with the reasonable hope and anticipation that patient outcomes would improve.

When considering the role of *JNNP* in such a process, in addition to immediate impact, the journal's current high standing has been built up over close to a century of publishing the world's seminal neuroscience publications.¹ As proof of longevity and ongoing relevance, akin to opening bottles of wine from an established cellar for the palate of the connoisseur, the success of the journal's immense archive

built up from 1920 is reflected through our achievement of the longest citation half-life of any journal across the clinical neurosciences. In other words, the original *JNNP* manuscripts continue to be heavily cited, many in the thousands,^{2,3} with some notching up more than 10 000 citations,⁴ further serving to reinforce the journal's standing as a neuroscience trailblazer.

How then does a manuscript become highly cited, a critical work from which others model and further develop their theories and practice? To help us understand the process, in this issue of *JNNP* we launch **Impact Commentaries** (figure 1), a monthly series which will provide a modern perspective on some of the most highly cited *JNNP* papers of all time. Where possible, we have approached the authors of the original study. In those instances where the author is no longer alive, we have asked key opinion leaders to comment on the original science and subsequent course of the findings presented, to decipher the reasons behind the success of each publication. In addition to providing pearls of wisdom, these commentaries provide newcomers, such as neurology trainees, with an opportunity to put the discoveries and developments into an historical context. Unfortunately, it is all too rare to have the opportunity to get the 'long view' from the original author of research that in retrospect has been a blockbuster. With our new monthly **Impact Commentaries**, we will focus on the opinions that set the scene and then go beyond the research study to discover how it influenced important developments in the field, in some cases over many decades—a perspective that newcomer journals are unable to provide.



Figure 1 Impact Commentaries, launched in this month's issue, provide a modern perspective on the most highly cited *JNNP* papers of all time.

While looking at impact from the past, *JNNP* continues to be excited about the future. Our ultimate goal is to identify key new developments and potential future discoveries in the constantly evolving world of neuroscience. The past year has seen *JNNP* receive more than 3000 submissions, although the higher submission rates inevitably generate greater selectivity. Already, a significant proportion of these recently published manuscripts, covering the entire realm of clinical neuroscience, are well on the way to becoming citation classics in their own right.^{5–16} Add to this reviews from experienced clinician researchers, regular podcasts and the recently launched *JNNP* blog, and a very 21st century notion of 'impact' begins to develop.

Borrowing a sentiment from the musician Brian Eno, once you've shocked, you can't shock again with the same tune. This year at *JNNP* we will be embracing that old rocker's conviction by both examining why the papers that shaped the world of neuroscience did so and seeking out the future classics that will make their 'impact' on the brain and mind sciences. We look forward to an exciting and challenging year ahead.

Competing interests None.

Provenance and peer review Commissioned; not externally peer reviewed.

Accepted 28 October 2011

J Neurol Neurosurg Psychiatry 2012;**83**:1–2.
doi:10.1136/jnnp-2011-301738

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The expanding phenotype of CLIPPERS: is it a disease or a syndrome?

Jun-ichi Kira

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a newly named pontine-centric inflammatory disorder.¹ The cardinal feature of the disease is punctate gadolinium enhancement 'peppering' the pons on MRI. The unique MRI features of this disorder have attracted many neurologists' attention leading to the publication of several case reports recently.^{2–5} The biopsied pontine pathology from the original study revealed a marked perivascular and parenchymal CD3-positive T-cell inflammation without any specific pathology.¹ However, because of the lack of a specific biomarker and long-term follow-up, the nosological position of CLIPPERS is still to be established.

The paper by Simon and colleagues⁶ (see page 15) reports five additional cases of CLIPPERS with detailed pathology and long-term evaluation, expanding the clinical, neuroimaging and pathological phenotype of this disorder: (1) cognitive impairment was seen in four of five cases along with cerebral atrophy in three of them; (2) MRI lesions were distributed not only in the pons but also in the brachium ponti and cerebellum, which

later culminated in severe atrophy of the cerebellum and brachium ponti; (3) prominent CD4-positive T lymphocytic as well as histiocytic infiltrates were observed, involving both small arteries and veins but with few B cells. Neuro-axonal injury was also found but there was no evidence of vasculitis (destruction of the vessel wall with fibrinoid necrosis).⁶ Based on the distribution of MRI lesions, Simon and colleagues propose an amendment of the disorder to chronic lymphocytic inflammation with *pontocerebellar* perivascular enhancement responsive to steroids (CLIPPERS).⁶ Lesions may occur in the spinal cord, basal ganglia or cerebral white matter. The perivascular gadolinium enhancement pattern and steroid-responsiveness indicate the autoimmune/inflammatory nature of this condition. These authors⁶ and others¹ carried out extensive laboratory and pathological surveys to exclude specific causes for the condition, such as sarcoidosis, histiocytosis, lymphoma, granulomatosis, multiple sclerosis, isolated angiitis of the central nervous system, Lyme disease, Whipple disease, Bickerstaff brainstem encephalitis, Behcet's disease and Sjögren's syndrome, suggesting that CLIPPERS is an independent disease entity.

However, there appears to be some overlap with other autoimmune/inflammatory brainstem-predominant encephalitis, especially brainstem type of neuro-Behcet's disease and Sjögren's syndrome. Pittock and colleagues¹ found no evidence of systemic illness; however,

Simon and colleagues⁶ reported additional subclinical systemic findings in some cases, namely antinuclear antibody SS-A, lymphocytic conjunctival infiltrate, lymphocytic sialadenitis and parotid uptake on gallium scan. Neuro-Behcet's disease is well known and frequently affects the pons and cerebellum. This disease occasionally presents without apparent mucocutaneous-ocular manifestations,^{7, 8} showing progressive cerebellar ataxia and prominent pontine and cerebellar atrophy. Such patients can also benefit from early steroid therapy. Cognitive impairment, first described by Simon and colleagues⁶ in CLIPPERS, is also frequently encountered in Behcet's disease. On MRI, enhancement of lesions in the pons and middle cerebellar peduncles frequently shows a mottled non-confluent pattern similar to that of CLIPPERS.^{9–11} At the chronic stage, severe atrophy of the basis pontis and cerebellum is common. Pathologically, Behcet's disease shows perivascular infiltration of T cells and macrophages/monocytes with few B cells, mainly involving venules but also occasionally small arteries.¹² Examinations of needle reaction, HLA-DR51 and interleukin 6 in the cerebrospinal fluid are essential to differentiate brainstem type of neuro-Behcet's disease from CLIPPERS. So far, all cases with CLIPPERS have been reported from Western countries. Behcet's disease is prevalent in Mediterranean countries, the Middle East and Japan. It is interesting to know whether there is any racial preponderance for this condition.

Cerebellar and brainstem involvement has also been repeatedly reported in Sjögren's syndrome,^{13–15} while sicca symptoms may not be clinically overt. MRI features of brainstem involvement in primary Sjögren's syndrome occasionally presents punctate gadolinium-enhancing foci peppering the pons, middle cerebellar peduncles, cerebellar hemispheres and vermis, and mesencephalon, which are quite similar to those of CLIPPERS.¹⁵ The subclinical involvement of exocrine glands found in some CLIPPERS cases⁶ suggests

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