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Letters to the Editor

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Immunosuppression during synaptogenesis a cause for childhood neurodevelopmental disorders

Corresponding Author:
Christopher J Pavlovski
Level 19, 2 Market Street
Sydney NSW 2000 Australia
Email: christopher.pavlovski@yahoo.com.au

Dear Editor:

This letter suggests that new studies are required into the notion that inadequate immune system capability during the period of synaptogenesis may be harmful causing neurodevelopmental disorders, possibly due to perturbations in neurochemical balance.

While the immune system is well known for protecting the human body from viral infection and bacterial threats, more recently it is understood to have a protective role in brain function and development with evidence indicating proteins associated with the immune system may play an additional role in normal brain development.[1] Previous work has indicated that essential fatty acid deficiency (a factor in immunosuppression), and more broadly the immune system itself may be compromised at birth.[2,3] This letter suggests that the immune system has a crucial protective role in neural circuit development, particularly during synaptogenesis, and a capable immune system ensures a stable metabolic environment for synaptic growth, strength, and axon pruning. Moreover, it is suggested that immunosuppression leads to metabolic imbalances that alter the pattern of synaptic pairing and growth leading to neurodevelopmental disorders.

A variety of factors contribute to immunosuppression including exposure to chemicals, dietary behaviour, and other factors.[3] For an immune system that may be already weakened at birth, a single insult or multiple insults may reduce or overload the immune system to function below a threshold that is able to provide an adequate protective role to support desired neurodevelopment. This may explain contradictions in previous work to pinpoint the exact cause of many neurodevelopmental disorders, since the causative factors may be more directly linked to immunosuppression, which in turn alters the expression of synaptic plasticity, growth, and pairing.

The intention of this letter is to refer to the wider set of metabolic functions associated with the immune system, rather than suggest that a specific immune actor such as lymphocyte dysfunction, or neural injury sustained from infection due to immune failure, is the sole causative relationship with disorders. Hence the immune system factors may include: cytokines balance and production, gut function, lymphatic system, adrenal system, inflammatory posture, neurotransmitter and hormonal balance, regulation system, allergic response, cellular apoptosis, etc. These ideas build upon previous work drawing the relationship between the broad set of immunological disturbances and neurodevelopment. More specifically, the complex set of immune actors that may be related to immunosuppression resulting in disturbances in chemical homeostasis and hence impact neural circuit development, particularly during the period of synaptogenesis. It is suggested that these relationships be the subject of new studies.

The ability to quantify the immune system of infants and children at key developmental milestones may provide a crucial opportunity to take preventative and remedial action to reverse immunosuppression, enabling the infant to adequately combat insults and maintain a stable environment for neurodevelopment. These milestones may be at birth, upon presentation of behavioural symptoms, and prior to key clinical interventions. Hence it is proposed that new studies be initiated to quantify the relationship between immunosuppression and neurodevelopmental disorders. Adopting trials such as immune related newborn screening[3] would provide the foundation for gathering such data.

Sincerely,

CJ Pavlovski

Conflicts of Interest
None to declare.

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Routine B12 testing for psychiatric admissions is no longer warranted

Corresponding Author:
Dr Anousha Pamela Woods
Barwon Health
Email: anoushawoods@gmail.com

Dear Editor:

The use of serum cobalamin (vitamin B12) as a screening test for psychiatric inpatients remains controversial,[1] as the poor diagnostic accuracy of the test continues to be recognised.[2] At present, there is no single gold-standard test to accurately diagnose true cobalamin deficiency and currently, serum cobalamin is the most commonly used investigation.[2] However, a meta-analysis and systematic review on the diagnostic performance of the test has revealed its inaccuracy, with a low test specificity and to a greater extent, sensitivity.[2] With this knowledge, we wanted to evaluate the clinical utility of the investigation as a psychiatric screening test within the regional healthcare service of Barwon Health. Barwon Health Human Research Ethics Committee (reference 12/102) approved this research.

A retrospective study was undertaken on all patients admitted to the psychiatric inpatient unit between August 2008 and May 2012. During that time, Barwon Health implemented serum cobalamin as a mandatory screening test for all newly admitted psychiatric inpatients. An analytical evaluation was undertaken to assess the clinical utility of implementing the screening test, where the medical records of patients with recognised low serum cobalamin were analysed to uncover whether this result altered their medical treatment. Furthermore, as defined by Garnier et al., [3] a "clinically relevant result" was identified if the treating team attributed a causal relationship between the deficiency and the patient's symptomatology. Cost effectiveness of the screening test was subsequently calculated using the method proposed by Acre-Cordon[4] (Table 1).

Table 1: Cost effectiveness of serum cobalamin as a psychiatric inpatient screening test at Barwon Health

Test	Total Tests	No. of low results	NNSAR	Cost per test	DCSAR
Serum Cobalamin	1,285	45 (3.5%)	28.6 patients	$18.45*	$526.84

NNSAR: Number Needed to Screen to find one Abnormal Result = 1 / prevalence of abnormal resul [4]
DCSAR: Direct Cost Spent to find one Abnormal Result = NNSAR x cost per test[4]
**St John Of God supplied direct cost of one serum cobalamin test*

There were 1,285 serum cobalamin tests completed between August 2008 and May 2012, of which 45 (3.5 per cent) revealed below reference range results. As seen in Table 1, the number needed to screen to find one abnormal result was 28.6 patients and the direct cost spent to find one abnormal result was AUD $526.84. Only 17 of the 45 patients received cobalamin therapy in conjunction with other psychiatric treatment, yet all deficient patients had documented mental state improvement over their admission. Despite treatment, it was revealed from the medical records that not one treating team attributed the patients' mental illness to their low serum cobalamin result. Therefore, the number needed to screen to find a "clinically relevant" abnormal result was theoretically infinite.

Previous studies that have endorsed serum cobalamin screening for psychiatric patients have often based their argument on a high prevalence of cobalamin deficiency in this population.[1] However, the findings of our robust study are supported by Lerner et al.[1] who compared serum cobalamin results of patients admitted to a psychiatric unit (n=225) with mentally healthy controls. Their study found no significant difference in cobalamin prevalence between the two cohorts, and thus recommended against the use of serum cobalamin as a screening test in this setting.[1]

Our study found that although only 17 patients received cobalamin therapy, all 45 patients with low serum cobalamin showed mental state improvement over their

admission. A similar result was found by Brett and Roberts,[5] who evaluated all low serum cobalamin results in a population of psychiatric inpatients (n=162). It was revealed in their study that of the 10 patients with a low result, four received no cobalamin therapy but had complete psychiatric resolution.[3] However, it is recognised in the literature that accurate assessment of psychiatric response to cobalamin therapy is challenging, due to varied therapy regimes and objective response criteria.[1,2]

The predominant limitation to our study was its retrospective design, which relied on accurate documentation by the treating teams. Another limitation of our research involved the lack of a standardised serum cobalamin reference range used amongst all institutions. This led to issues when attempting to compare the prevalence of low serum cobalamin results between different studies.

In summary, our study has demonstrated the poor clinical utility of measuring serum cobalamin in all newly admitted psychiatric patients. We found no clinical benefit of using serum cobalamin as a screening test, with low prevalence of abnormal results and no causal relationship found between the deficiency and psychiatric illness. The poor diagnostic accuracy of the test[4] and the financial burden involved further supports our conclusion not to perform serum cobalamin as a routine screening test on the inpatient psychiatric population.

Sincerely,

Dr Anousha Pamela Woods
House Medical Officer, Austin Health
145 Studley Road Heidelberg, VIC 3084, Australia

A/Prof Richard Harvey
Mental Health, Drugs and Alcohol Services, Barwon Health
Bellarine Street, Geelong, VIC 3220, Australia

Conflicts of Interest

None to declare.

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"Newborn bloodspot screening policy framework for Australia": An update

Corresponding Author
Prof Craig White
Newborn Bloodspot Screening Working Group of the Standing Committee on Screening,
c/o 189 Royal St, Level 3C
Perth, WA, 6004
Email: NBSWG@health.wa.gov.au

Dear Editor,

Newborn bloodspot screening (NBS) is an essential public health initiative, which has delivered benefits to Australian families for more than 50 years. While these programmes are highly successful, they are currently at a crossroads and clear direction and processes are needed to support their continued success. There is increasing pressure to add new conditions to NBS programmes, and new technologies and opportunities are on the horizon.[1] Given the changing environment, it is essential that Australian NBS programmes remain a priority for policy makers. In line with this, in the past year there have been a number of calls for a national policy framework for NBS,[1,2] including most recently by O'Leary and Maxwell in your journal.[3]

O'Leary and Maxwell[3] highlight the need for a policy framework to assess conditions for inclusion in NBS programmes. The article describes activities undertaken by governments to develop such policy guidance. In doing so, the authors refer to the work of the Australian NBS Working Group, suggesting that it has been "slow"[3] and does not fully address the policy issues facing NBS. As chair of the NBS Working Group, I can respond to these claims in an informed manner and provide an update of the policy environment of NBS in Australia.

Specifically, I wish to highlight that in the past few months Australia's first *Newborn Bloodspot Screening National Policy Framework* has been submitted to governments for their consideration. This has been thanks to the enormous amount of work completed by the Working Group, which for those involved in the process was by no means slow. Further, the policy framework draws upon a range of evidence, including extensive stakeholder input. As such, it provides a thoroughly considered policy response to the gaps that exist for NBS.

The NBS Working Group was established in March 2014 specifically to develop a national policy framework for NBS. The Working Group was founded by the Standing Committee on Screening, which falls under the remit of the Australian Health Ministers' Advisory Council. In the 18 months following its establishment, the Working Group met 14 times, held two national workshops, hosted an online survey, sought targeted input from key stakeholders and actively provided regular updates for all stakeholders. Through these approaches, the experience of more than 450 people informed the policy development process. The Working Group also comprehensively considered academic literature, international NBS policies, relevant Australian policies, including those on screening and quality and safety, and practices of local newborn and other screening programmes.

The aim of the policy framework is to provide uniting guidance for NBS in Australia, and respond to key policy issues. It does so by articulating policies that guide programme strategic direction and operations, quality and safety, monitoring and evaluation, and decision making. Importantly, the draft policies take into account the real world experience of NBS and the Australian health system. This means that the policy framework is the best possible for the Australian environment. Key examples of this are recommendations relating to governance, information sharing, decision making, and monitoring and evaluation; which advocate for a national approach, but support continued state and territory management and funding of the programmes. This combination is the only viable model that draws upon existing structures and expertise, reduces duplication and builds consistency.

The *Newborn Bloodspot Screening National Policy Framework* is a landmark step in the programmes' histories, which we anticipate will be considered for adoption by all Australian governments this year. The policy framework will put in place mechanisms agreed by Australian governments to seize opportunities and conquer challenges for programmes to ensure future success. While not an endpoint itself, the policy framework is a significant and historic major step towards the further development of what is already a strongly performing programme. It recommends a clear governance model that can support future policy or programmatic change. Further, the policy development process has brought people together with the common goal of supporting NBS. In doing so, the process has started a dialogue between programmes, governments, consumers, and others that will ensure Australian families are provided access to the best possible programmes now and into the future.

I hope that the above provides clarity on the current policy environment for NBS. More importantly, I hope it provides readers a sense of optimism for NBS, knowing that a significant policy milestone is soon to be achieved that will support the programmes into the future.

Sincerely,

Craig White

Clinical Associate Professor
Chair, Newborn Bloodspot Screening Working Group of the Standing Committee on Screening

Conflicts of Interest

Prof White is Chair of the Newborn Bloodspot Screening Working Group of the Standing Committee on Screening.

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