Australian Government
Repatriation Medical Authority

REPATRIATION MEDICAL AUTHORITY

STATEMENT OF REASONS

S 196B(9) *VETERANS' ENTITLEMENTS ACT 1986*

DECISION NOT TO AMEND THE CURRENT STATEMENTS OF PRINCIPLES CONCERNING MOTOR NEURONE DISEASE FOLLOWING A REVIEW

Instrument Nos. 67 & 68 of 2013

PART I INTRODUCTION

1. The Repatriation Medical Authority (the Authority) pursuant to subsection 196B(9) of the *Veterans' Entitlements Act 1986* (the VEA), has decided not to amend the Statements of Principles concerning motor neurone disease Instrument Nos. 67 and 68 of 2013, following an investigation which was notified in the *Commonwealth of Australia Gazette* on 10 January 2017.

2. The Authority concluded that the new sound medical-scientific evidence available to it is insufficient to justify an amendment to Statements of Principles Instrument Nos. 67 and 68 of 2013, already determined in respect of motor neurone disease.

PART II BACKGROUND TO THE INVESTIGATION

3. A request dated 3 October 2016, was received from "a person eligible to make a claim for pension under Part II or Part IV of the *Veterans' Entitlements Act 1986* ('the VEA')", seeking a review into "traumatic brain injury" and "blows to the head" as factors in the balance of probabilities Statement of Principles concerning motor neurone disease determined under subsection 196B(3) of the VEA.

4. The balance of probabilities Statement of Principles Instrument No. 68 of 2013, concerning motor neurone disease does not have any factors relating to "traumatic brain injury" and "blows to the head". Factors relating to "traumatic brain injury" and "blows to the head" are included in the reasonable hypothesis Statement of Principles concerning motor neurone disease, Instrument No. 67 of 2013, determined under subsection 196B(2) of the VEA. The applicant requested that the factors relating to head injury that are currently included in the reasonable hypothesis Statement of Principles be included in the balance of probabilities Statement of Principles on the grounds of natural justice, logic and fairness.

5. On 6 December 2016, the Authority, under subsection 196B(7A) of the VEA, decided to review the contents of the Statements of Principles Instrument Nos. 67 and 68 of 2013, to find out if there was new information in respect of "traumatic brain injury" and "blows to the head" as factors in motor neurone disease.

6. The Authority received a further email submission on behalf of the applicant, dated 5 December 2016, comprising the five published peer-reviewed papers below. The first two papers had previously been considered by the Authority, while the other three had been published since the previous investigation concerning motor neurone disease.

    - McKee AC, Gavett BE, Stern RA, et al (2010). TDP-43 proteinopathy and motor neurone disease in chronic traumatic encephalopathy. J Neuropathol Exp Neurol, 69(9): 918-29.

    - Weisskopf MG, O'Reilly EJ, McCullough ML, et al (2005). Prospective study of military service and mortality from ALS. Neurology, 64(1): 32-7.

- Weisskopf MG, Cudkowicz ME, Johnson N (2015). Military service and amyotrophic lateral sclerosis in a population-based cohort. Epidemiol, 26(6): 831-8.

- Seals RM, Hansen J, Gredal O, et al (2016a). Physical trauma and amyotrophic lateral sclerosis: a population-based study using Danish National Registries. Am J Epidemiol, 183(4): 294-301.

- Seals RM, Kioumourtzoglou M-A, Hansen J, et al (2016b). Amyotrophic lateral sclerosis and the military: a population-based study in the Danish Registries. Epidemiol, 27(2): 188-93.

7. The investigation notice was signed by the Chairperson of the Authority on 20 December 2016 and was gazetted in accordance with section 196G of the VEA in the *Commonwealth of Australia Gazette* on 10 January 2017. Submissions were invited from persons and organisations wishing to make a submission by 17 March 2017.

PART III SUBMISSIONS RECEIVED BY THE AUTHORITY PURSUANT TO SECTION 196F

8. Following notification of its investigation, the Authority did not receive any information from persons eligible to make submissions pursuant to section 196F of the VEA.

PART IV EVIDENCE/INFORMATION AVAILABLE TO THE REPATRIATION MEDICAL AUTHORITY

9. The following information was available to the Authority:

9.1. The information held by the Authority and obtained during its previous considerations leading to the determination of Statements of Principles concerning motor neurone disease, Instrument Nos. 67 and 68 of 2013.

9.2. Literature searches were conducted using the Ovid search engine from 1996 to April Week 2 2017, limited to English language. The search terms were: head injury.mp. or Craniocerebral Trauma/ AND Amyotrophic Lateral Sclerosis/ or Motor Neuron Disease/. Sixteen articles were retrieved. Articles were selected based on relevance, study quality, reliability and journal authority. The above search was supplemented by PubMed searches for Amyotrophic Lateral Sclerosis/ or Motor Neuron Disease and head injury, internet searches and manual searches of reference lists.

9.3. Medical or scientific publications as set out in the bibliography attached hereto.

9.4. A briefing paper concerning motor neurone disease prepared for presentation to the Authority by a Medical Researcher of the Secretariat.

PART V SOUND MEDICAL-SCIENTIFIC EVIDENCE

10. The Statements of Principles are determined on the basis of the available "sound medical-scientific evidence" as defined in section 5AB(2) of the VEA which states:

"*Information about a particular kind of injury, disease or death is taken to be* ***sound medical-scientific evidence*** *if:*

(a) the information:

(i) is consistent with material relating to medical science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or

(ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

(b) in the case of information about how that kind of injury, disease or death may be caused - meets the applicable criteria for assessing causation currently applied in the field of epidemiology."

PART VI REASONS FOR THE DECISION

11. Several lines of evidence have been used to assess the association between head injury and risk of motor neurone disease. There are studies concerning head injury per se, and also studies of military personnel and athletes, particularly football players.

12. In relation to studies examining head injury as the risk factor, a key issue is how head injury was measured. Where head injury measurement is based on self-report in a retrospective study, there is a risk of recall bias (i.e., recall of the risk factor is increased in cases compared to controls because cases have the disease). To address the problem of recall bias, other studies have used medical records as objective data on head injury. Studies using self-report of head injury have often found positive associations, whereas those using objective measures of head injury have not found positive associations.

13. Another key methodological issue in studies of head injury and motor neurone disease is the chronological association between head injury and onset of motor neurone disease, as motor neurone disease itself is likely to cause falls and head injury (reverse causation). This may occur in the prodromal phase, before motor neurone disease is diagnosed. Hence, many studies exclude the traumas occurring up to 5 years before the date of diagnosis of motor neurone disease.

14. In the meta-analysis by Wang et al (2016), 13 of the 17 estimates on which the analysis was based were positive, with a meta relative risk for all trauma of 1.73 (95% CI 1.43-2.09). The size of the meta-relative risk for head trauma specifically was smaller, with the lower bound of the confidence interval approaching the level of no effect (OR 1.27, 95% CI 1.02–1.57).

15. For reasons that were unclear, a number of case-control studies published before 2016 were not identified and included in the meta-analysis by Wang et al. One of the case-control studies that was not included used self-report of "severe" traumatic brain injuries and also found a significant positive association (Seelen et al 2014). Three other case-control studies that were not included in the meta-analysis used medical record data to

assess head injury and did not find an association between head injury and motor neurone disease (Peters et al 2013, Turner et al 2010, Williams et al 1991). An additional case-control study published in 2016 used hospitalisation date to identify trauma and found no association between head trauma and motor neurone disease when traumas prior to the index date were excluded (Seals et al 2016a).

16. It has also been suggested that head injury might worsen motor neurone disease. However, Fournier et al (2015) found no difference in the rate of decline of motor neurone disease between patients with and without head injury. Two studies using rodent models of motor neurone disease (Thomsen et al 2015, Evans et al 2015) found no association between a single head injury and disease onset or survival, although the latter found that mild traumatic brain injury negatively impacts muscle denervation and motor performance, possibly potentiating the clinical effects of motor neuron pathology.

17. A second line of evidence relates to observations of motor neurone disease occurring in military populations. An association between motor neurone disease and military service has been observed in some studies, although it has not been consistent. Of eight studies which examined associations between motor neurone disease and military service, four studies (three case-control studies and one cohort study) found an increase in risk (Haley 2003, Horner et al 2003, Weisskopf et al 2005, Seals et al 2016b). The first two studies were in veterans of the first Gulf War only.

18. Four studies (three cohort studies and one case-control study) did not find an overall increase in risk of motor neurone disease with military service, except in relation to older conflict zones. One US cohort study found no significant overall increase in risk associated with military service compared to those without military service, and a significant increase only with service in World War II (Weisskopf et al 2015). Similarly, a recent US study found significant associations only with service in World War II and Korea in cases compared to controls (Beard et al 2016). A US cohort study of Gulf War veterans found no increased risk of motor neurone disease compared to non-Gulf War veterans (Barth et al 2009). One small cohort study of the French military with possible underascertainment of cases found a decreased risk overall compared to the general population, but an increase in the 50-54 year age group (Drouet et al 2010).

19. A particular concern about an increase in risk of motor neurone disease in Gulf War veterans had earlier been raised by Haley (2003) and Horner et al (2003). However, Weisskopf et al (2015) found no increase in risk of motor neurone disease in theatres of war subsequent to World War II, Beard et al (2016) found no increase in risk of motor neurone disease in theatres of war subsequent to the Korean War and Barth et al (2009) found no increase in risk of motor neurone disease when comparing Gulf War and non-Gulf War veterans. Two studies found that the increased risk of motor neurone disease in deployed Gulf War veterans had returned to that of controls after ten years (Horner et al 2008, Seals et al 2016b). This pattern could suggest a temporary increase in risk, or bias from patterns in health service usage in recently discharged veterans, or discharge from the military due to prodromal or overt motor neurone disease.

20. A methodological problem with most of these studies of military populations is lack of data on exposures, including head injury, and a lack of control for smoking, a suspected risk factor for motor neurone disease. In an attempt to study possible military

exposures, Beard et al (2016) questioned subjects about 37 possible military exposures.

21. In this study, motor neurone disease was positively associated with exposure to herbicides for military purposes, nasopharyngeal radium, personal pesticides, exhaust from heaters or generators, high-intensity radar waves, contaminated food, explosions within one mile, herbicides in the field, mixing and application of burning agents, burning agents in the field, and Agent Orange in the field, with odd ratios between 1.50 and 7.75. Limitations of this study include recall bias, validity of responses (especially for exposures occurring decades ago or restricted to particular theatres of conflict), correlation of exposures with each other, and statistically significant results occurring by chance due to multiple comparisons. It was unclear whether a traumatic brain injury did actually occur in subjects reporting "explosions within one mile".

22. A third line of evidence relates to observations of motor neurone disease occurring in populations of athletes, particularly Italian soccer players and US football players (Beghi 2013). Autopsy case series have also found that around 10% of athletes with chronic traumatic encephalopathy also had motor neurone disease (McKee et al 2010, Daneshvar et al 2015). However, not all studies have found increases in risk of motor neurone disease or specific pathology in association with sporting activity. One community-based study of footballers did not find an association with motor neurone disease, although there were only 2 cases (Savica et al 2012). One series of 47 motor neurone disease autopsy cases found no significant differences in histopathology in those with and without head injury (Fournier et al 2015).

23. As with the military studies, data are lacking concerning the relevant exposure in sporting populations. Postulated risk factors include repeated concussions, exercise-associated hypoxia, use of substances or dietary supplements, pesticides and smoking in later life. There are several features of the available data which point to the possibility that soccer players with motor neurone disease are susceptible individuals who develop the disease in response to combinations of environmental factors (Beghi 2013). The predominance of bulbar-onset motor neurone disease among soccer players is in clear contrast with the site of onset of the disease in the general population, in which bulbar-onset motor neurone disease is age-related and tends to be less frequent in males than in females. The mean age of onset of motor neurone disease among soccer players is also significantly lower than expected for sporadic motor neurone disease. Soccer players are a selected population, chosen on the basis of neuromuscular ability. Complex genetic and environmental factors can influence physical stamina and fitness.

24. The co-occurrence of chronic traumatic encephalopathy and motor neurone disease does not mean that they are causally related, and much is still unknown about the prevalence and risk factors for chronic traumatic encephalopathy. More rigorously designed studies in unselected populations are needed to understand the association between sport and both chronic traumatic encephalopathy and motor neurone disease. Daneshvar et al (2015) concluded that factors needing further assessment in relation to chronic traumatic encephalopathy include gender, age at first exposure, number, timing and severity of head injuries, cognitive reserve and flexibility, substance use and neuropsychiatric comorbidities.

25. Overall, while some studies have found positive associations between motor neurone disease and head injury, and some studies have found a high prevalence of motor neurone disease in specific populations (athletes and military personnel), the evidence that such associations indicate that head injury is a cause of motor neurone disease is limited in a number of ways. These limitations include possible bias in the study designs, inconsistency in the findings, a lack of association in studies with less risk of bias, the possibility of reverse causation, the possibility of confounding by other risk factors (especially smoking and genetic propensity) and lack of assessment of the severity and timing of head injury.

26. The VEA requires that the same body of evidence be assessed according to two different standards of proof. For assessment under the reasonable hypothesis standard (s 196B(2)) the VEA requires that the sound medical-scientific evidence must indicate or point to a causal association between a risk factor and the disease in question. On the other hand, for the balance of probabilities standard (s 196B(3)), the sound medical-scientific evidence must show that it is more probable than not that there is a causal association between a risk factor and the disease. In this matter the distinction between those standards of proof is significant.

27. The available sound medical-scientific evidence indicates or points to a causal association between "traumatic brain injury" and "blows to the head" and motor neurone disease, such being sufficient to support a judgement of a possible causal association. The reasonable hypothesis standard is met and an appropriate factor is included in that Statement of Principles.

28. However, as detailed in the reasons set out above, the sound medical-scientific evidence does not show that it is more probable than not that there is a causal association between "traumatic brain injury" and "blows to the head" and motor neurone disease. The available evidence is therefore insufficient to support a judgement of a probable causal association between "traumatic brain injury" and "blows to the head" and motor neurone disease and the balance of probabilities standard cannot be met. In these circumstances no factor can be included in that Statement of Principles.

PART VII DECISION

29. At its meeting on 7 June 2017 the Authority decided not to amend the Statements of Principles in respect of motor neurone disease for the purposes of subsections 196B(2), (3) and (8) of the VEA as the Authority concluded, for the reasons set out above, that the new sound medical-scientific evidence available to it is insufficient to justify an amendment to the Statements of Principles already determined in respect of motor neurone disease.

Professor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

30 June 2017

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