Sports Concussion and Category Mistakes

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At the conclusion of their thoughtful discussion of sports concussion and chronic traumatic encephalopathy (CTE), Kelly et al. commit a category mistake.[1, 2] They assert that more "neuroscientific evidence" is needed for prevention strategies. Designing prevention measures is a policy issue and the evidentiary standards for policy decisions and establishing scientific certainty are different.[3] Rational policy-making is a decision analysis procedure assessing likely benefits and harms of policy choices.[4] Designing a prevention strategy to mitigate the potential consequences of repetitive sports-related head impacts is straightforward. Any sports where recurrent head impacts are unavoidable - boxing, mixed martial arts, American football, rugby – would be abandoned. The rules of sports such as association football can be modified to markedly reduce the risk of head impacts.

As Kelly et al. state, "A wealth of evidence supports the notion that physical trauma to the brain can have deleterious effects on cognition, mood, and motor function, and it is probable that multiple blows to the head are more harmful than one alone." What would our society lose by eliminating sports involving multiple head impacts? These sports provide two social services – entertainment and participation opportunities for the young. Are we justified in exposing even a small number of individuals to the risk of serious injury for entertainment? The answer is surely no. Sports participation has definite health and social benefits for the young. Can we find less risky substitutes? The answer is surely yes. In a decision analysis framework, we have little to lose and may have much to gain with a straightforward prevention strategy.

Kelly et al. propose sophisticated longitudinal studies to explore interesting questions about sports concussions and CTE. Their dedication to scientific rigor is admirable but short-sighted. As they point out, resolving some of questions they discuss could take many years. Evaluating potential interventions derived from these kinds of studies would also take many years. Indeed, given that long-term consequences of recurrent head impacts may occur decades later, truly rigorous observational and intervention studies are probably impossible. This is a case where the requirements for scientific certainty invite paralysis.

We already have enough data to formulate rational policy. As a community, clinical neuroscientists should advocate an end to boxing, mixed martial arts, American football, and rugby. We should also advocate significant modification of the rules of several other sports.

Potential Conflicts of Interest

None declared.

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Type I Interferon Signature in *NOTCH1*-Related Leukoencephalopathy

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We read with great interest the article "Heterozygous *NOTCH1* Variants Cause CNS Immune Activation and Microangiopathy," written by Dr Helman and colleagues. The authors identify heterozygous de novo gain-of-functions variants in *NOTCH1* as causative of leukoencephalopathy with calcifications in 7 unrelated patients.[1] Neuroimaging features suggested inflammatory microangiopathy similar to Aicardi–Goutières syndrome (AGS), with increased cerebrospinal fluid IP-10 levels in 3 of 4 analyzed patients.[1]

While the article was in the process of being published, we found by trios whole exome sequencing the novel c.4811 T > G (p.Val1604Gly) de novo heterozygous missense variant in *NOTCH1* (NM_017617.5), classified as likely pathogenic according to the American College of Medical Genetics and Genomics criteria[2] (PM2, PS2, and PP3), in a 2-year-old boy affected by poor cognitive and motor development, congenital macrocephaly (birth: 38cm, >97th percentile; 2 years: 51cm, >97th percentile), ureteropelvic junction stenosis, and magnetic resonance imaging features of leukoencephalopathy with calcifications and cysts (Figure A–H). Central hypotonia and delay in developmental milestones were evident in the first months of life; fever-induced focal motor seizures started from the age of 9 months, leading to diagnostic investigations. Neurological examination showed fair eye contact, babbling, truncal hypotonia with incomplete head control, appendicular spasticity with pyramidal signs, and exaggerated startle response to auditory stimuli. After neuroimaging, full metabolic and TORCH screening, and fundus oculi and cardiological evaluation were all normal.

Due to neuroimaging similarities with AGS, we investigated the peripheral blood type I interferon (IFN) score and