

REVIEW ARTICLE

Anti-NMDA Receptor Encephalitis, Vaccination and Virus

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Abstract: Anti-N-methyl-D-aspartate (Anti-NMDA) receptor encephalitis is an acute autoimmune disorder. The symptoms range from psychiatric symptoms, movement disorders, cognitive impairment, and autonomic dysfunction. Previous studies revealed that vaccination might induce this disease. A few cases were reported to be related to H1N1 vaccine, tetanus/diphtheria/pertussis and polio vaccine, and Japanese encephalitis vaccine. Although vaccination is a useful strategy to prevent infectious diseases, in a low risk, it may trigger serious neurological symptoms. In addition to anti-NMDA receptor encephalitis, other neurological diseases were reported to be associated with a number of vaccines. In this paper, the anti-NMDA receptor encephalitis cases related to a number of vaccines and other neurological symptoms that might be induced by these vaccines were reviewed. In addition, anti-NMDA receptor encephalitis cases that were induced by virus infection were also reviewed.

Keywords: Anti-NMDA receptor encephalitis, neurological symptom, H1N1 vaccine, tetanus/diphtheria/pertussis, and polio vaccine, Japanese encephalitis.

1. INTRODUCTION

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis was first characterized by Dr. Dalmau and his colleague [1] in 2007. This is an acute autoimmune disorder exhibiting a well-defined set of clinical symptoms. Patients may have initial psychiatric symptoms, and then develop a multistage illness from memory disturbances, catatonia, seizures, movement disorder, loss of consensus, and hypoventilation. At the early stage, this disease may be misdiagnosed as a psychosis disease because of primary psychiatric disorders. In addition, infective encephalitis is taken more into consideration at first due to the unawareness of this disease. The misdiagnosis may delay proper treatment intervention and might lead to an unsatisfactory outcome.

The pathology of this disorder is that the patients' own antibody attacks the NMDA receptor in the brain. The disease mechanism is that the GluN1 subunit of the NMDA receptors in the brain is targeted by autoantibodies [2]. The cause of this autoimmunity is usually unknown. However, a lot of cases were reported to be related to tumors. Teratomas, especially ovarian teratoma, have been detected in a portion of patients, and tumor removal is significantly associated with a good outcome. The autoimmunity occurred because the immune system should attack the tumors, but mistakenly attack the brain.

This disease may not be diagnosed early because patients' initial psychiatric symptoms such that this disease might be misdiagnosed as psychosis in an early stage. An accurate diagnosis of anti-NMDA receptor encephalitis requires the detection of anti-NMDA antibodies in the serum or spinal fluid of an individual. Currently, this disease can be diagnosed using a test developed at the University of Pennsylvania. In general, adequate treatment can improve patient outcomes. Therefore, an early diagnosis is an important factor for a good prognosis of this disease.

2. CAUSE

It was reported that anti-NMDA receptor encephalitis was induced by vaccination. Although vaccination is the most effective

way to prevent infectious diseases, the issue of whether vaccines can cause chronic diseases such as asthma, multiple sclerosis, chronic arthritis, and diabetes has been discussed [3]. Vaccination with live-attenuated polio vaccine may cause poliomyelitis occasionally [4]. Autoimmune diseases might be caused by the immunization induced by vaccination because some microbial proteins are similar to human proteins [5], and the immune system might respond to self-proteins [6, 7]. A number of anti-NMDA receptor encephalitis cases were associated with vaccination, including H1N1 vaccine, tetanus/diphtheria/pertussis, and polio vaccines and Japanese encephalitis vaccine [8-10].

Tumors may trigger the anti-NMDA receptor immune response and induce this disease. Many cases were reported to be associated with tumors, especially ovarian teratoma [1, 11]. The association of ovarian teratoma and anti-NMDA receptor encephalitis usually occurs in young women [12]. After resection of the ovarian teratoma and followed by prompt treatment, clinical conditions usually can be remarkably improved [13, 14].

In addition to ovarian teratoma, many cases were reported to be associated with other tumors, including hepatic neuroendocrine carcinoma [15], a large-cell neuroendocrine carcinoma [16], mature mediastinal teratoma [17], testicular teratoma [18], and small cell lung carcinoma [19]. A study compared anti-NMDA receptor encephalitis teratomas with control teratomas containing neuroglial tissue from women without anti-NMDA receptor encephalitis. The result showed that anti-NMDA receptor encephalitis teratomas were significantly smaller and were composed of a higher percentage of neuroglial tissue than control teratomas [20].

Virus infection can induce anti-NMDA receptor encephalitis. Herpes simplex type 1 encephalitis (HSE) is encephalitis that predominantly affects temporal lobes. After recovery, a portion of children with HSE encephalitis developed anti-NMDA receptor encephalitis [21-23]. NMDA receptor antibodies were identified in 5 prospectively diagnosed patients with relapsing post HSE [21]. 3 patients had a relapsing course with chorea after HSE had elevated autoantibodies against NMDA receptor [22]. This yielded the hypothesis that the inflammatory destruction of neural tissue resulted in the reactivation of autoreactive lymphocytes against NMDA receptor antigens and the production of pathogenic anti-NMDA

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receptor encephalitis antibodies [24]. A prospective observational study of 54 patients and a retrospective study of 48 patients in another group were conducted to investigate the risk that HSE triggered autoimmune encephalitis [25]. The results showed that autoimmune encephalitis occurred in 27% of patients with HSE.

3. TREATMENT AND PROGNOSIS

This disorder is an autoimmune disease. There are several immunotherapies for this disease. Steroids, intravenous immunoglobulin (IVIG) and plasma exchange (or plasmapheresis) constitute the first-line immunotherapies; rituximab and cyclophosphamide are the second-line immunotherapy [26-29]. Tumor resection is a useful treatment for patients with tumor [30, 31]. Most patients are initially treated with steroids. A study showed treatment effects and outcomes in 501 patients. 472 patients that underwent first-line immunotherapy or tumor removal resulted in improvement within 4 weeks in 251 patients. For the other 221 patients, 125 received second-line immunotherapy that resulted in a better outcome than those who did not [32]. They concluded that most patients responded to immunotherapy and the second-line immunotherapy was usually effective when the first-line treatments fail. In addition, the effects of different combinations of therapies, including IVIG, plasma exchange (or plasmapheresis), rituximab (or cyclophosphamide) and tumor resection are discussed. A study of 94 patients including 18 male patients and 76 female patients collecting from the literature showed that treatment combinations including at least two of these categories resulted in higher efficacy rates than treatment with a single form of therapy [30].

Patients with more involuntary movements, disturbance of consciousness, central hypoventilation, and accompanying hypoalbuminemia and pulmonary infection may respond poorly to first-line treatments and therefore second-line immunotherapy needs to be considered [33]. For male patients without tumor, the efficacy rate of plasmapheresis (or plasma exchange) may not be inferior to those of intravenous immunoglobulin and rituximab (or cyclophosphamide) [33]. The findings from the first autopsy performed on a man with anti-NMDA receptor encephalitis were reported. Severe testicular damage was additionally observed in this male patient. These findings suggest similar brain pathology in patients of both sexes and severe testicular damage in male patients [34].

The recovery of anti-NMDA receptor encephalitis can take from several months to several years after disease onset [32]. About 80% of patients can achieve a good outcome within 24 months of disease onset [32], and some patients largely recover within approximately one year [30, 33]. To predict one year functional status in patients, a score associated with 5 factors, intensive care unit admission, treatment delay >4 weeks, lack of clinical improvement within 4 weeks, abnormal magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) white blood cell count >20 cells/ μ L, was proposed to estimate the clinical course following diagnosis. This score may identify patients who could benefit from novel therapies [35].

4. VACCINES

Vaccines are one of the most successful medical advances to prevent diseases. However, no vaccine is completely free of adverse effects. Although evidence for an association between vaccination and illness may not be strong, many people still make a conscious decision not to vaccinate. Also, parents increasingly question the necessity of immunizing their children [36]. Although the usual adverse effects of vaccines only involve local reactions, such as pain and erythema, the severity reaction might involve neurological disorders, such as anti-NMDA receptor encephalitis. The following are the vaccines discussed in the literature shown to be related to anti-NMDA receptor encephalitis.

5. H1N1 VACCINE

The H1N1 vaccine was discovered to associate with narcolepsy. Hypocretin is a neuropeptide associated with wakefulness and loss of hypocretin-producing neurons may cause narcolepsy [37]. H1N1 vaccines were shown to block a receptor for hypocretin because of a peptide from a nuclear protein in the H1N1 virus itself that mimics the hypocretin receptor [38]. Incidence of narcolepsy occurs and increases after the pandemic H1N1 influenza vaccination in many countries [39, 40]. There was a consensus that an increased risk of narcolepsy was consistently observed after Pandemrix (AS03-adjuvanted) vaccine [41]. The risk for narcolepsy following exposure to the H1N1 pandemic vaccine is highly dependent on the index date for disease onset. The risk for narcolepsy in younger patients was increased 14 times during the first year, three times elevated the second year, but with no detectable increased risk more than 2 years after vaccination exposure [42]. An association between Pandemrix and narcolepsy was observed during the A/H1N1pdm09 pandemic, and a role of a CD4 T cell mimicry sequence in the haemagglutinin protein of A/H1N1pdm09 cannot be excluded [43]. A non-coding RNA gene GDNF-AS1 was found to associate with Pandemrix-induced narcolepsy, and changes in the regulation of GDNF have been associated with neurodegenerative diseases [44]. Several countries have observed an association between narcolepsy and H1N1 vaccines. Nevertheless, no substantial association between the use of H1N1 vaccines and narcolepsy was identified in Taiwan [45]. Incidence rates of narcolepsy in Taiwan, Canada, and Europe following exposure to pandemic H1N1 virus or vaccination were discussed, and incidence rates of narcolepsy varied by age, continent, and period [45].

A retrospective analysis was performed to examine unsolicited adverse events in an integrated safety set comprised of 10784 children, and 373 children were at risk of influenza complications [46]. Incidences of adverse birth and pregnancy outcomes of pregnant women immunized with seasonal (TIV) and H1N1 vaccines were studied. The incidences include preterm birth (<37weeks), very preterm birth (<32weeks), low birth weight (<2500 g, LBW), very low birth weight (<1500g), small for gestational age and spontaneous abortions were discussed [47]. Women who went on to deliver preterm showed a significantly greater flu vaccine response for the H1N1 strain than women who delivered at term [48]. A correlation with spontaneous abortion in women who received the H1N1 influenza vaccine was identified [49, 50]. The safety of inactivated influenza vaccines in pregnancy for birth outcomes was discussed [51].

Guillain-Barré syndrome (GBS) is a serious acute demyelinating disease that may cause paralysis. GBS remains the most frequent neurological condition reported after influenza vaccination including swine influenza vaccination [52]. Another study revealed that GBS should be considered an infrequent adverse effect of influenza vaccination [53]. No significant effect of the 2009-2010 H1N1 influenza or vaccination against it for GBS occurrence was observed [54]. The 2010/11 influenza vaccine implied an increased GBS risk. However, surveillance of the identical vaccine in the 2011/12 influenza season did not find an increased GBS risk after vaccination [55]. The rate of GBS reported following monovalent influenza vaccination was higher in the military than civilian [56]. Despite underlying reporting bias in 2010-2011, an increase in GBS incidence over background GBS, was unlikely related to A(H1N1)pdm09 influenza immunizations [57]. Two patients developed anti-NMDA receptor encephalitis after vaccination against H1N1 influenza [8, 9].

6. TETANUS/DIPHtherIA/PERTUSSIS AND POLIO VACCINES

Diphtheria, tetanus, and pertussis (DTaP) are three bacterial diseases that can be vaccinated against with a single shot. The fourth dose of DTaP vaccine might increase the incidence of fever

and injection site reactions compared with the first dose and one out of 30 children had the symptom of swelling of the thigh or upper arm up to seven days after the fourth or fifth dose [58]. Reduced antigen DTaP vaccination is included in the maternal immunization program in Brazil, and no increased risk of pregnancy-related adverse events was found following maternal vaccination with DTaP [59]. A natural language processing algorithm was developed to identify local reactions associated with the DTaP vaccine [60]. A study investigated whether the live measles, mumps, and rubella vaccine compared with the non-live diphtheria-tetanus-acellular-pertussis-inactivated-polio-Haemophilus influenza type b vaccine was associated with fewer acute hospital contacts for childhood asthma among boys and girls [61]. A 15-year-old female patient developed a low-grade fever and general fatigue after a booster vaccination against tetanus, diphtheria, pertussis, and poliomyelitis. Later, she was diagnosed with anti-NMDA receptor encephalitis by the detection of anti-NMDA receptor antibodies in plasma and CSF [8].

7. JAPANESE ENCEPHALITIS VACCINE

The U.S. Vaccine Adverse Event Reporting System (VAERS) received 300 adverse event reports following inactivated mouse brain-derived Japanese encephalitis (JE) vaccination (24 per 100,000 doses distributed) from 1999 to 2009. Among these cases, 106 were classified as hypersensitivity reactions and 4 were classified as neurologic events. Among them, 23 reports serious adverse events. There were no reports of encephalitis, meningitis, or Guillain-Barré syndrome [62].

Since 1989, an unusual number of systemic reactions following JE vaccination were reported from Australia, Canada, and Denmark, 860 German travelers were recruited during a period of 16 months for a prospective study to investigate the incidence of side effects following JE vaccination. 65 travelers were reported to have systemic side effects like headache, fever, dizziness and generalized rash [63]. 10 adult travelers from Denmark developed moderate-severe neurological symptoms within a few weeks of JE vaccination. Three patients initially had symptoms varying from severe encephalitis-like illness to paraesthesia, double vision or parkinsonian gait disturbance, and they might develop acute disseminated encephalomyelitis (ADEM) or multiple sclerosis. Several patients had symptoms such as long-lasting headache, concentration difficulty, intellectual reduction, afebrile convulsions, and depression. A woman developed myelitis [64]. A 2-year-old girl had confirmed anti-NMDA receptor encephalitis by the detection of anti-NMDA receptor antibodies in CSF after receiving a JE vaccination [10]. In addition, cases of allergic reactions to JE vaccine are discussed in the literature, and Tables 1 and 2 list some of these cases [65].

Table 1. Passive reporting of allergic, mucocutaneous reactions to inactivated Japanese encephalitis vaccine.

Type of Reaction	Country and References
Urticaria	Denmark [66], Australia [67], United Kingdom [68], Japan [69]
Erythema multiforme	Denmark [66]
Rash	Denmark [66]
Urticaria/angioedema	Australia [44], Denmark [70],
Cutaneous/respiratory	Japan [71]
Systemic eruptions	Japan [72]
Urticaria/edema	Japan [72], United States [72]

Table 2. Questionnaire studies of allergic, mucocutaneous reactions to inactivated Japanese encephalitis vaccine.

Type of Reaction	Country and References
Urticaria	Canada [73]
Universal itching	India [74]
puffy eyes	India [74], United Kingdom [75]
arthralgia	United Kingdom [75]
Generalized rash	Germany [63]
Eye swelling	United States [76]

The cases of anti-NMDA receptor encephalitis related to vaccination reported in the literature are summarized in Table 3.

Table 3. The cases of anti-NMDA receptor encephalitis and vaccination.

Patient	Age	Vaccine or Virus	References
one female patient	15	tetanus, diphtheria, pertussis, and poliomyelitis	[8]
two patients	-	H1N1	[9]
one patient	-	H1N1	[77]
one female patient	2	Japanese encephalitis vaccine	[10]

8. HERPES SIMPLEX VIRUS

Herpes simplex virus-induced anti-NMDA receptor encephalitis has been well-described. Two cohorts in a case-control observational study were performed to determine whether there is an association between nonencephalitic herpes simplex virus 1 (HSV-1) infection and anti-NMDA receptor encephalitis. Past HSV-1 infection was found in significantly more anti-NMDA receptor encephalitis cases than controls [78]. Observing a 3-year-old girl who suffered from anti-NMDA receptor encephalitis after the resolution of HSE, it revealed that Cytokine/chemokine elevation during the transition phase from HSE to autoimmune anti-NMDA receptor encephalitis [79]. The post-HSE anti-NMDA receptor encephalitis inflammatory response was more pronounced than the anti-NMDA receptor encephalitis [80]. Post-HSE relapses have been recently associated with autoimmunity driven by antibodies against NMDA receptors [81]. Patients who experience new or recurrent neurological symptoms following recovery from HSE should be evaluated for post-infectious anti-NMDA receptor encephalitis [82]. The pathophysiologic mechanisms by which HSV infects neurons may produce a higher likelihood of contracting anti-NMDA receptor encephalitis [83]. The Epstein-Barr virus is one of human herpesvirus type in the herpes family. Pathogenic examinations revealed positive Epstein-Barr virus (EBV)-nuclear antigen, EBV-capsid antigen (CA)-IgG antibodies, and positive EBV-early antigen (EA)-IgG antibody in 3 cases after the diagnosis of anti-NMDA receptor encephalitis [84].

9. JAPANESE ENCEPHALITIS VIRUS AND HUMAN PAPILLOMAVIRUS

Compared with the well-description of HSV inducing anti-NMDA receptor encephalitis, findings on Japanese encephalitis virus (JEV)-induced anti-NMDA receptor encephalitis are rare. A

7-year-old boy was diagnosed with JE, and four weeks after the onset of JE, the patient presented with anti-NMDA receptor encephalitis symptoms. Antibodies against NMDA receptors were detected and immunotherapy led to significant recovery [85]. In addition, JE can trigger the anti-NMDA receptor encephalitis. Samples of CSF for three patients who had confirmed JE and then developed relapsing symptoms characterized by movement disorder and/or behavioral problems were examined for anti-NMDA receptor immunoglobulin G (IgG), and all of the three samples were positive for anti-NMDA receptor IgG [86]. Two cases of anti-NMDA receptor encephalitis were reported to be possibly triggered by JE [86, 87].

Human papillomavirus (HPV) vaccination prevents infections with HPV that cause most cervical cancers. Cases of adverse events following HPV vaccination have been reported [88-90]. Suspected adverse events after HPV vaccination include postural orthostatic tachycardia syndrome, chronic fatigue syndrome, complex regional pain syndrome, headache and orthostatic intolerance [91]. A female patient developed postural tachycardia syndrome after HPV vaccination and was examined with positive serum anti-NMDA receptor antibodies [92].

10. MICRORNA BIOMARKERS

MicroRNAs (miRNAs) were first discovered in the early 1990s while studying development in the nematode *Caenorhabditis elegans* [93, 94]. miRNAs are single-stranded, non-coding RNAs of about 22–24 nucleotides that play important roles in the regulation of gene expression, cell proliferation, differentiation and apoptosis and physiological processes [95]. There have been many computational methods developed to predict gene targets of miRNA [96-100]. miRNA expression is dysregulated in human malignancies. In cancer development, miRNA expression is dysregulated in human malignancies that miRNA functions as a tumor suppressor or an oncogene by targeting specific genes [101]. The first research studying abnormalities in miRNA expression in tumor samples focused on B-cell chronic lymphocytic leukaemia (B-CLL) that this tumor suppressor activity is likely provided by two miRNAs, miR-15a and miR-16-1 [102]. Circulating microRNAs play an important role in cancer diagnosis, tumor subtype classification, and outcome prognosis. For non-small cell lung cancers (NSCLC), plasma miRNA such as miR-21-5p, miR-20a-5p, miR-141-3p, miR-145-5p, miR-155-5p, and miR-223-3p have been identified to be differentially expressed in different stages of disease and to contribute to the diagnosis, treatment determination, and prognosis [103]. miR-21 was found to be up-regulated in glioblastomas, breast, colon and pancreatic cancer and has been appointed as an oncogenic miRNA [104].

miRNA also may contribute to neurological diseases and inflammation in the brain [105]. Two miRNAs, miR-34a and miR-504 as well as their downstream pathways were identified to account for amyotrophic lateral sclerosis (ALS) pathological mechanisms and represent potential therapeutic targets [106]. By applying the principle component analysis based unsupervised feature extraction, 107 miRNAs are selected to be related to ALS [107]. In addition to ALS, miRNAs are related to Parkinson's disease (PD) and many miRNAs are identified to target genes associated PD [108-115]. For other neurological diseases, there are many studies for their miRNA biomarkers; miR-663a, miR-502-3p, miR-206, miR-124, miR-132, miR-922, miR-516a-3p, miR-571, miR-548b-5p and miR-548c-5p are related to frontotemporal dementia [116-119]; miR-107, miR-9, miR-124a, miR-125b, miR-128, miR-26b, miR-144, miR-29, miR-34, miR-181, miR-106, miR-146a, miR-132 and miR-153 are associated with Alzheimer's disease [108, 120-125]; miR-9, miR-206, miR-132, miR-183, miR-335-5p, miR-431 and miR-375 are related to spinal muscular atrophy [126-130].

Compared with other neurological disorders, the miRNA biomarker for anti-NMDA receptor encephalitis has not been discussed as well as the other diseases in the literature. Nevertheless, a study showed that significant down-regulation of let-7a, let-7b, let-7d, and let-7f was observed in anti-NMDA receptor encephalitis patients and especially let-7b is the potential to be used as diagnosis and prognosis biomarker for the anti-NMDA receptor encephalitis [131]. let-7 has also demonstrated to be involved in cancer development that is expressed at low levels in lung cancer tissue compared to normal tissue and the expression of let-7 correlates with lung cancer survival [132]. The miRNAs related to these discussed vaccines or viruses are summarized in Table 4, that is an extension result from the literature [10].

11. PHYLOGENETIC TREE

The phylogenetic tree analysis has been widely used in the miRNA study [149-154]. It has been successfully used in finding cancer miRNA biomarkers and the association between vaccines and anti-NMDA receptor encephalitis [10, 100].

A procedure of using the phylogenetic tree approach was proposed in a study [155] to explore the association between anti-NMDA receptor encephalitis and vaccines or virus based on miRNA biomarker.

This phylogenetic tree method has been used to explore the association between JE and anti-NMDA receptor encephalitis [10]. It might be very difficult to design an experiment to study the effect of vaccines on the anti-NMDA receptor encephalitis. Therefore, the phylogenetic tree might be a useful bioinformatics analysis to explore the relationship between vaccine and autoimmune disease.

Table 4. miRNA biomarker of anti-NMDA receptor encephalitis, vaccine, and virus.

Disease, Vaccine or Virus	miRNA Biomarker	References
anti-NMDA receptor encephalitis	let-7a, let-7b, let-7d, and let-7f	[131]
pertussis,	miR-202, miR-342, miR-206, miR-487b, miR-576	[135]
poliomyelitis	miR-555	[4]
H1N1	miR-323, miR-491, miR-654, miR-10a, let-7a, let-7c, miR-31, miR-29a, miR-148a, miR-146a	[136-139]
herpes simplex virus	miR-145, miR-101	[138, 140]
Japanese encephalitis virus	miR-19b-3p, miR-33a-5p, miR-155, miR-29b, miR-146a	[141-143]
human papillomavirus	miR-29a, miR-143, miR-145, miR-218, miR-496, miR-22	[144-148]

In the above procedure, the main tool is using miRNA biomarkers to plot the phylogenetic tree. Although this approach can be used to explore the association between vaccine and disease, the accuracy might depend on their miRNA biomarkers. On contrast, another approach is to plot the phylogenetic tree of vaccine virus and bacteria nucleotide sequences. Using this method, there might be difficult in finding a virus or bacteria nucleotide sequence representing a disease because a disease might not be induced by a virus or bacteria. Nevertheless, when the virus that is closely related to this disease can be found, the phylogenetic tree of the virus or bacteria sequences can be directly used to explore the relationship between the vaccine and the disease.

CONCLUSION

Anti-NMDA receptor encephalitis is a serious disorder and difficult to diagnose. Patients who are diagnosed early and treated properly have a good prognosis. To prevent the relapse of this disease, exploring the factors that cause this disorder is important. A number of cases have been reported to be related to vaccination such as H1N1, Tetanus/diphtheria/pertussis and polio, and Japanese encephalitis vaccinations. Many cases caused by vaccination may not have been reported. More studies of vaccination-related cases can provide useful information for the prevention of anti-NMDA receptor encephalitis. In addition to anti-NMDA receptor encephalitis, this paper also discusses other neurological disorders caused by vaccines as well as anti-NMDA receptor encephalitis. More advanced studies on exploring the pathology of these adverse events are needed to evaluate the safety of these vaccines.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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