

EDITORIAL

Some aspects about the clinical and pathogenetic characteristics of the presumed persistent measles infections: SSPE and MINE

Paul Richard Dyken

Institute for Research in Childhood Neurodegenerative Diseases, Mobile, Alabama, U.S.A.

It is well known that Subacute Sclerosing PanEncephalitis (SSPE) is due to an aborted form of the wild measles virus which results from a faulty immune reaction of the human body (1). The pathogenesis of this particular slow virus disease begins when an immunologically incompetent individual is attacked by the virus and is thereby unable to launch a full immune response, allowing parts of the aborted virus to harbor in the central nervous system. As is typical of all slow virus diseases, the aborted virus remains quiescent for a number of months to years only to break out to produce the neurological and ophthalmic symptoms of SSPE. The major components of the disease results from the progressive deterioration of the host's nervous system, first starting with sometimes subtle and nonspecific higher cortical symptoms such as abnormal behavior, learning disabilities, single epileptic seizures and visual disturbances which formulate in months into a characteristic clinical period called stage I. Then the near diagnostic period of repetitive massive myoclonic jerks, beginning mental failure, motor disability in its early stages and immobility are seen which constitutes what has been called stage II. This stage is also progressive and in a few months the involuntary movements disappear and the dementia worsens. Stage III is a nonambulatory state of clinical affairs with ultimately complete motor failure, loss of the previously seen involuntary

movements and severe dementia. Stage IV represents a severe "vegetative" stage which plateaus to severe neurological disability of at least 90% or death. This typical clinical progression is closely correlated with a rostral-caudal neural destruction. Most of what is thought to be clinically typical about this disease, is a manifestation of the neuropathological and clinical happenings which occur in stage II. This stage represents the classical subacute progressive clinical picture of what I call the subacute progressive form (SPF) of SSPE. There are other more atypical forms of the disease. The classical or SPF form and presentation represents only about 75% of the cases of SSPE which has been reported to the USA/World SSPE Registry since 1989.

In the 1960s, in the heyday of SSPE and natural measles in the USA, about 60 cases of SSPE were reported per year whereas there were over 500,000 cases of natural measles infections reported, giving a ratio of 1 case of SSPE to 10,000 cases of measles exanthema. After the first national immunization program against measles was initiated in this country in the early 1960s, measles began to drop in frequency. There is usually a 7 to 10 year latent or interval period in the development of SSPE after the first contact with the wild measles virus. After correcting for the interval period, SSPE was also shown to drop in frequency (2). Because of these phenomena, other countries began to develop national immunization programs, and they soon found, in most instances, that mass immunization produced similar dramatic results.

In the USA, it is generally believed that SSPE is a figment disease of antiquity. It is true that only 80 cases of SSPE has been reported to the Registry by USA physicians in the last 15 years. Yet, because of the disease's well worked out mechanisms of etiology, pathogenesis and near elimination, understanding is of great importance, to USA pediatric neurologists and other health care workers. This understanding is even of greater importance to the health care workers in developing

Correspondence: Paul Richard Dyken, M.D., MLA, BS.
Director of the USA/World SSPE
Registry since 1980 Offices located in
Institute for Research in Childhood
Neurodegenerative Diseases
283 Wingfield Drive
Mobile, Alabama, 36607, U.S.A.
Tel: 1 251-478-6424, fax: 1 251-476-8277.
E-mail: pdyken@aol.com
Received: June 4, 2004.
Accepted: June 5, 2004.

and developed nations outside of the USA where the incidence of this disease is at present greater than in the USA. It is particularly important because, in spite of a declining incidence due to effective national measles immunization programs, these mechanisms of disease may be an explanation for entirely new or unrecognized disorders with similar pathogenesis and etiology. In other words, other diseases of similar nature, such as the progressive childhood neurodegenerative diseases, specifically and generally, may also be caused by similar mechanisms. It goes without saying that the childhood neurodegenerative diseases of unknown or uncertain cause represent a large portion of any practice of pediatric neurology in both the "developed" and the "developing" nations of the world.

The relationship of SSPE to persistent measles infection is well established, but the second syndrome discussed in this paper is not. The syndrome (3) that I call MINE (Measles Induced Neuroautistic Encephalopathy) is properly categorized as a childhood neurodegenerative disease but with uncertain etiology. In the last few years, this syndrome has been shown to be related to the live measles vaccination, if not proven to be caused by it. The syndrome was first recognized in the late 1990s by Wakefield et al. (4), a gastroenterologist in Britain. What was initially described was a syndrome consisting of chronic recurrent enterocolitic symptoms starting in young children. These patients also seemed to have chronic neurological symptoms which were considered to be autistic in nature. Wakefield et al. (4) considered the syndrome to be related to the immunization of infants with live-attenuated measles vaccine. Over the following years, approximately 2000 children with variants of this autistic-colitic syndrome were reported. Because of my interests in SSPE, I was able to carefully evaluate 12 of these patients, sharing the patient's clinical information and full laboratory data with the Solicitor firm (5) which handled the rather large class action suit resulting from these reports.

Altogether, the key features of this syndrome were not always associated with both enterocolitis and pervasive developmental disorder. In the review of 12 patients, two major varieties of the syndrome were identified, one with pure neuroautistic features (n=4) and the second with additional chronic recurrent enterocolitis (n=8). In addition to at least two of the four classic symptoms of autism (i.e. defects of intellect, behavior, social adjustment and language development), the children who were evaluated had other neurological symptoms such as epileptic seizures, micrencephaly, dysgenetic features and rarely progressive mental retardation which would more rightly be considered to be frank

dementia. Both of these variations, that is, the pure neuroautistic and the neuroautistic/enterocolitic patients seemed to be induced by the live-attenuated measles virus vaccination, after a latency period of several months. In each patient, regardless of type, measles virus genes were found in the tissues studied, such as blood, gut and spinal fluid. In those with enough antigen identified, the genes were found to arise from the vaccine-related live-attenuated measles virus and not from the usual wild measles virus which is associated with measles exanthema. The two viruses have the same antigenic make-up. The proteins are the same but one of them is wildly alive and the other is alive but attenuated.

These are the constellation of features which make up the MINE syndrome

1. All the patients have had a live-attenuated measles vaccination between 12 and 21 months of age; at this time none of the children showed any neuroautistic features or preliminary signs of enterocolitis;
2. All of the patients developed neurological-behavioral symptoms many months after the initial measles immunization (i.e. an interval period is characteristic of all slow viral diseases) which for the most part were autistic in nature;
3. Prior to vaccination there was a history of severe, recurrent infection or frank allergy, suggesting that each patient had some sort of pre-existing immunological problem, prior to the immunization and the neurological symptoms;
4. There was a history in all patients of some sort of familial suspected dysgenetic or inherited problem such as schizophrenia, 21 trisomy or birth defects; one patient, a girl, had the clinical characteristics of Rett syndrome (6) and gene analysis showed a defect in the location of the MECP2 gene (7) which has been associated with this syndrome; this was the only female in the series and the only one who had micrencephaly, all others had larger than the mean "for-age-and-gender" head sizes on routine measurement of the occipito-frontal circumference; the gene analysis features in the female suggested a defective gene mechanism which might predispose a susceptible patient to the effects of the live-attenuated measles virus in spite of the fact that the clinical effects of both Rett and MINE are quite similar; none of the males showed any evidence for a known gene-related disorder;
5. Only 67% (n=8) of the population studied had a history of chronic, recurrent enterocolitis in addition to their neuroautistic symptoms;
6. 92% (n=11) of the 12 patients were male, an interesting fact since male predominance also features the cousin disease, SSPE; all of the males showed normal male chromosome karyotypes and all had head measurements which were larger but less than 2 standard deviation above the mean for

occipito-frontal circumferences for their age and gender;

7. Recurrent, severe epileptic seizures and a developmental dysphasia occurred in one of the patients and he was considered to have the Landau-Kleffner syndrome (7), and in others both epileptic seizures and language and speech problems were frequently present;

8. Although all the patients had at least two of the four characteristics of the autistic spectral syndrome, some had only mild forms such as in two brothers who were considered to have Asperger's syndrome (9); some had the full extent of the autistic syndromes including progressive loss of cognitive skills emblematic of Heller infantile dementia (10); most had all the characteristics of the children Kanner (11) described in 1943;

9. All of the patients studied had measles genes identified by molecular genetic studies from the enterocolon, blood, and spinal fluid, although none of them had had clinical symptoms suggesting that they ever had contact with the measles virus except through the live-attenuated measles immunization which each of them received; furthermore in situations where there was enough measles antigen present more sophisticated molecular genetics were performed which identified the vaccine-related form of the measles virus gene distinguished from the more virulent wild measles virus gene;

10. None of the children had brain postmortem studies or had received brain biopsies.

An opinion can be given that MINE develops in the same fashion as does SSPE. Although the syndromes are different the etiology and the pathogenesis are similar. For both syndromes, two factors are required: an immature or defective immune system which is unable to inactivate the attacking measles virus whether it is the wild or the live-attenuated form. In the situation of SSPE the full antigenic wild virus is only partially inactivated, allowing the remaining, aborted form to escape and harbor within the large neurons of the cerebral cortex where they are sheltered and persist, to grow. Then, in years, the persistent virus breaks out, devastatingly inflames and destroys in a rostral-caudal fashion other neurons, endothelial cells, glial elements and cellular processes. It is presumed that in SSPE, susceptible patients have had contact with the wild measles virus before immunization if they are ever immunized. Yet, this is the reason the incidence of both measles exanthema and SSPE are dropping with the institution of effective national immunization programs. All data that has been accumulated suggests that measles immunization does not cause SSPE, but the opposite occurs. In the situation of MINE, the child has not been exposed to the wild measles virus yet but instead is immunized with a much less virulent but

antigenically comparable live-attenuated measles virus. Most individuals become immune to the wild measles virus when the live-attenuated one is given them, but a relatively small portion of them react in a different fashion. This small portion is judged to be 1 in 10,000; based on the fact that in Britain about 20,000,000 children have been immunized in the last 20 years and about 2,000 have developed the MINE syndrome. Those who develop MINE do not completely neutralize the live-attenuated virus and an aborted form of the virus ensues. The aborted form escapes and harbors in the nervous system in particularly susceptible areas such as the hippocampus, limbic system and older portions of the cerebral cortex where the blood-brain barrier is less protective, especially in the temporal-limbic areas where dysfunction may be important in the formation of the clinical features of the various autistic syndromes. Opposed to the lengthy period of quiescence seen in SSPE when the "escape" of the aborted, partially damaged wild measles virus acts upon the larger neurons residing in neocortical areas, the interval period in MINE is only a matter of months. It would appear that "break-out" is not as devastating as in SSPE and the clinical symptoms after the short interval may be more due to chronic sapping of the selected host cell's metabolic activity. Although this pathogenesis explains the neuroautistic symptoms of MINE, it does not explain the often associated enterocolonic symptomatology. Since vaccine-related measles genes are found in the enterocolon literally years after the immunization of an affected individual, it is probable, as opposed to the situation in SSPE, that some of the aborted live-attenuated virus harbors in gut as well, which periodically breaks out rather than harbor for long periods of time as occurs in SSPE.

There are many questions which are still unanswered about SSPE and MINE. Yet, there is still enough known to identify the syndromes as real ones. Certainly the recognition of the MINE syndrome represent at least one explanation for the increased incidence of the infantile pervasive disorders in the so-called developed nations of the world, but also the increase in learning disabilities, behavioral problems, seizure disorders and neurodegenerative diseases seen in the practices of most pediatric neurologists of the world.

References

1. Dyken PR. Neuroprogressive disease of post-infectious origin: a review of a resurging subacute sclerosing panencephalitis (SSPE). *Ment Retard Dev Disabil Res Rev* 2001; **7**: 217-225.
2. Dyken PR, Cunningham SC, Ward LC. Changing character of subacute sclerosing panencephalitis in the United States. *Pediatr Neurol* 1989; **5**: 339-341.

3. Dyken P. Descriptions of a new controversial pediatric neurologic syndrome. *J Child Neurol* 2004; **19**: 296 (Abstract).
 4. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-641.
 5. Alexander Harris Solicitors, Inc. London, England.
 6. Rett A. Ueber ein eigenartiges hirnarropfes syndrome bei hyperammonaemie im kinderalter. *Wien Med Wschr* 1966; **116**: 723 (in German).
 7. Xiang F, Zhang Z, Clarke A, et al. Chromosomal mapping of Rett's syndrome: a likely candidate region on the telomere of Xq. *J Med Genet* 1998; **35**: 297-300.
 8. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. *Neurology* 1957; **7**: 523-530.
 9. Filipek PA. Asperger's disorder. In: Swaiman KF, Ashwal S (eds). *Pediatric Neurology. Principles and Practice* (3rd ed). St. Louis: Mosby, 1999, pp 610-611.
 10. Heller T. Ueber dementia infantilis. *Z Erkorsch Behandl Jugendl Schwach* 1908; **2**: 17 (in German).
 11. Kanner L. Autistic disturbances of affective contact. *Nerv Child* 1943; **2**: 217.
-