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ENCEPHALITIS FOLLOWING MODIFIED MEASLES

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In 1958 Riley[1] reported two cases of encephalitis following measles that had been modified by prophylactic injections of gamma globulin. He also referred to the reports of three previous authentic cases and to twelve possible cases which were not documented. The purpose of this communication is to report two additional cases, consider any pertinent information which might clarify the unexpected occurrence of encephalitis following modified measles and to discuss the relation of this circumstance to the current use of measles vaccine.

Report of Cases

CASE 1 was a white male of four years and two months who was exposed to measles by his nine-year-old brother on April 10, 1963. On the basis of history this was established as the first day of contact. On April 15, 1963 he was given 0.9 ml (0.045 ml/Kg) of gamma globulin. On April 26, 1963 he complained that he did not feel good, became anorexic and vomited but was afebrile. On May 1, 1963 his eyes became red and he developed a few spots on his face. Cough was conspicuously absent but he did sneeze a few times. Physical examination on that day revealed a few red macules on the face and body, slight redness of the conjunctiva, moderate redness of the throat and a single white spot on the buccal mucous membrane. Oral temperature was 101.6F. Treatment consisted of sulfisoxazole 1.5 gm q 4 hours for two days. The temperature reached normal the following day and he had no further symptoms. At 7 a.m. on May 6, 1963 he got out of bed to go to the bath room, where he fell to the floor and was unable to get up. The parents reported that "his right side was involved but there was no shaking and he had a gurgle in his throat". He was taken to the emergency room of a nearby hospital where he received an injection and a suppository of phenobarbitol after which he seemed better. He was then admitted to this hospital.

Physical Examination: There was a positive Kernig's sign and minimal nuchal rigidity and a normal plantar reflex. The fundi were normal. The color was dusky and there was a fading rash noted on the face and chest. His sensorium was cloudy as evidenced by a lack of his usual sharpness in comprehending situations and interest in co-operating. He talked irrationally and was extremely irritable. His refusal to allow examination represented a marked change in personality. Temperature was 39.5°C. The remainder of the physical examination was negative. The admission spinal tap gave normal hydrodynamics.

Laboratory Findings: Spinal fluid WBC'c 33 (Polys 9, Monos 24), RBC's 3, Protein 61 mg per cent, Glucose 50 mg per cent, negative culture. Blood count: Hb 12.5 g, WBC 7,000, N 44, L 55, M 1. Blood Calcium 10.6 mg per cent, Phosphorus 3.3 mg per cent, Blood Glucose 79 mg per cent. Skull X-ray was negative. An EEG done on May 8, 1963 reported — "evidence of a severe diffuse cerebral disturbance throughout both hemispheres with peaks that suggest brain stem involvement". Urine was negative.

Course: Phenobarbitol was given to the patient in the afternoon of the admission day to control the irritability, but it stimulated him instead. He was then given diphenhydramine hydrochloride which did sedate him. At 10 p.m. that day he talked coherently but was still

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irritable. The next two days the nuchal rigidity was less and the temperature gradually subsided to normal. There was little other change. On May 9, 1963 the nuchal rigidity returned to the original degree, Kernig's sign and Brudzinski's sign were positive and the cremasteric and abdominal reflexes were absent. The deep tendon reflexes were not obtained. On May 10, 1963 the nuchal rigidity was again less and the deep tendon reflexes were obtained.

On May 13, 1963 he had improved considerably — his personality had returned to normal. The cremasteric and abdominal reflexes had returned, and there was only slight nuchal resistance to flexion. There was no neurological deficit. On May 15, 1963 he was discharged from the hospital in good condition.

Follow Up: A repeat EEG was made on June 27, 1963 which was reported as "normal for age". He was seen in the office July 7, 1963 at which time his mental condition was felt to be normal and there were no neurological signs. All deep and superficial reflexes were obtained normally. He was seen on several occasions for respiratory infections without any evidence of neurological or mental residuals. At the time of his last visit, January 4, 1964 he was still normal in every way.

* * *

CASE 2 was a three-year-old white female. History revealed that she was exposed to measles by an older sister on May 13, 1963. On May 16, 1963 she was given 0.4 ml of gamma globulin (Wt. 16.3 Kg). She was reported as being febrile off and on since May 20, 1963. A rash appeared back of the ears on May 24, 1963 and became general on May 28, 1963, at which time she "had a high fever". There was no cough. On June 3, 1963 she was drowsy for four hours in the morning, and after a deep sleep lasting one hour, she woke up vomiting. Her physician considered that she had a convulsion and referred her to this hospital.

Physical Examination: Patient was a well nourished white girl of about 16.3 Kg with a generalized severe macular rash. Her color was cyanotic. There was twitching of the left side of the mouth and the eyes deviated to the left. Her convulsive state persisted with twitching of the right thumb, arm, shoulder and right leg until controlled with IV sedation (Sodium Amytol 60 mg). Her sensorium was depressed to unconsciousness from the time of the convulsion until three hours later when she cried with painful stimuli. This gradually improved, and an hour later she called to her mother. At 2 a.m. next day her sensorium cleared and she talked coherently. An admission spinal tap gave normal hydrodynamics.

Laboratory findings: Blood count — Hb 10.5 g, WBC's 17,700, N 79, L 15, E 1 and M 5. Urine was normal. Spinal fluid — WBC's 21, Polys 12, Monos 9, Protein 47 mg per cent, Glucose 75 mg per cent. An EEG made June 6, 1963 showed evidence of cerebral disturbance in the left occipital parietal region.

Course: Treatment was carried out with intravenous fluids, sedation and hydrocortisone. A satisfactory recovery followed and she left the hospital June 8, 1963. A repeat EEG made on June 20, 1963 gave evidence of a moderate somewhat paroxysmal disturbance in the left temporal and posterior regions. This represented an increase in paroxysmal character from the first examination. A report from her personal physician indicates that up to the time of this report the patient is completely normal. Documentation of diagnosis in both cases is based on criteria of Tyler.[2]

COMMENT

We believe that the occurrence of measles encephalitis in patients whose measles was modified by gamma globulin assumes new significance because of the widespread interest in and use of measles vaccine to prevent or modify measles through active immunization. Fulginiti and Kempe[2] reported on 5,000 children who had received measles vaccine. Of this number, 632 were subsequently known to have been exposed to measles. Of these, 39 or 6.3 per cent developed unmodified measles, 73 or 11.5 per cent developed modified measles and 520, or 82.2 per cent did not develop recognizable measles. Their figures also indicate that the best immunization was obtained from the use of two injections of inactivated virus, followed by one injection of live virus, giving 87 per cent complete protection (no measles) 13 per cent partial protection (modified measles) and no case of unmodified measles. This may be a

matter of great importance in preventing encephalitis, as will be pointed out later, since the other two systems of immunization (one injection of live virus together with gamma globulin or three injections of inactivated virus) were both followed by a significant number of unmodified cases and more modified cases.

It is not unreasonable to assume that the immunity obtained from the administration of gamma globulin is similar to that produced actively by means of measles vaccine. In fact, Fulginiti and Kempe[3] state that:

> "The measles neutralizing antibody contained in pooled adult gamma globulin can modify both natural and live virus vaccine induced measles. This observation suggests that antibody invoked by inactivated vaccine might modify the reaction to live vaccine."

If this be true, then it would follow that inasmuch as the antibodies in gamma globulin are similar to, if not identical with, those produced by the active immunization of vaccine, the same type of failure might be anticipated from vaccine as was experienced with gamma globulin (the occurrence of measles encephalitis in patients whose measles had been modified by gamma globulin). This would present a gloomy outlook for measles vaccine were it not for the encouraging explanation for the failure of gamma globulin to protect the patient from encephalitis offered by Koprowski[4] in which he envisions the invasion of the central nervous system by the virus during the short period between exposure and the administration of the gamma globulin. In contrast, the protection afforded by vaccine will be present at the time of exposure and should prevent the virus from invading the central nervous system. The remaining probability of such invasion would be in those children who had not achieved complete protection from the vaccine, the 18 per cent pointed out by Fulginiti and Kempe.[3] However, of this group two thirds (12 per cent) did get partial protection in that they developed a modified measles. This immediately raises the question as to whether this amount of protection is sufficient to prevent nervous system invasion by the virus. These considerations are bound to influence the choice of vaccine to be used, for the expectation of protection against measles encephalitis will be greatest with that vaccine which is shown to give the highest percentage of prevention rather than just modification, at least until such time as modification is known to be equally effective in preventing the entrance of virus into the brain. For the present, the combination of two injections of inactivated virus followed by one of live seems to be preferred.

Of the two foregoing factors, 1) presence of antibody in the blood at the time of exposure, and 2) effectiveness of the immunity from the three different methods of vaccination employed, it is important to know the part each plays in the prevention of measles encephalitis. Clinical trial in a large series of vaccinees will probably give the answer, but it must be remembered that measles encephalitis is a relatively rare condition and it may require several years to produce sufficient data on which valid conclusions can be drawn. We recognize that other factors such as familial predisposition, previous central nervous system damage, possible differences in the

neurotropic propensities of different measles viral strains and others have been suggested as entering into the pathogenesis of measles encephalitis.

It would be interesting to know if encephalitis has ever occurred in a child who had been exposed to measles and received gamma globulin but did not develop clinical measles in any form. We are not aware of any such cases being reported but if timing or "hyperergy", as interpreted by Koprowski[4] is involved in measles encephalitis, they are certain to occur since clinical signs of measles may well be completely masked by gamma globulin given after invasion of the central nervous system.

The behavior of the superficial reflexes (abdominal and cremasteric) in case P.G. is interesting, particularly since a similar pattern was noted in another boy with measles encephalitis whose measles was not modified with gamma globulin but did occur in the same epidemic. In his case the reflexes were examined critically because P.G. had alerted us to the difference between the deep and superficial reflexes. His deep reflexes were present normally at a time when the abdominal and cremasteric were absent. It was also noted that when the patient improved clinically, the abdominal and cremasteric reflexes began to return. At first they were weak and easily fatigued, that is, after being elicited two or three times they would disappear for two to three hours, after which time the same reaction could be obtained. At the time of his last follow-up visit (seven weeks after the onset of the encephalitis) he seemed completely recovered and the superficial and deep reflexes were normal.

Summary

Two additional cases of measles encephalitis, after a modifying dose of gamma globulin, are being reported. A valid explanation of this undesired occurrence seems to us to be embodied in Koprowski's[3] interpretation of "hyperergy," the possibility of central nervous system invasion by virus, between exposure and administration of the gamma globulin. This early invasion should not occur in successful measles vaccination inasmuch as the protection is present at the time of exposure.

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