SOME UNUSUAL ASPECTS OF INFLUENZA IN PEDIATRICS *

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An influenza infection may produce several unusual manifestations outside of its expected localization in the respiratory tract. Definite recognition of these atypical forms must be based on biologic criteria.

Except among infants, where it is most often unreliable, the complement fixation test is a valuable biologic indication in the diagnosis of influenza. In Lyon, Sohier [1] has demonstrated the advantages of complement fixation as compared with the hemagglutination inhibition test or Hirst's reaction: the simplicity of the test, the earlier appearance of antibodies (after the seventh day of illness), and the certitude with which the nature of the infection is indicated.

With Sohier, we consider it significant when there is a fourfold increase in the titer of antibodies found in two specimens of serum taken ten days apart. When only one specimen is available, a positive result with a dilution of 1 : 64 is considered a definite indication of a recent infection. A positive result with a dilution of 1 : 32 is sometimes considered indicative if clinical evidence is in agreement.

With these criteria for selection and with the thousands of serologic tests of pneumotropic viruses performed in Professor Sohier's laboratory, we were able, in five years, to assemble 98 cases of influenza A and B from among the pediatric patients of Dr. M. Bernheim and Dr. M. Jeune in Lyon.

In 13 of the 98 cases, the influenza virus caused unusual manifestations quite independent of any secondary infections.

I. Influenzal Serofibrinous Pleurisy.

The frequency with which serofibrinous pleurisy of viral origin can be established has been discussed. [2] In fact, although the participation of the pleura, in the form of a dry pleural reaction, in influen-

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zal pneumonopathy is frequent (noted by us in 14 cases), and although pleurisy due to secondary infection, purulent or puriform, is not rare (5 cases in our statistics), we were able to find only one case of influenzal serofibrinous pleurisy.

Case 1. A small, asthmatic four year old boy, presented a severe serofibrinous pleurisy on the left side as far as the scapula. There was also a slight interbronchial adenopathy on the left. Culture and guinea pig inoculation of the fluid proved negative. Skin reaction to tuberculin was negative and remained so for a three year follow-up period. The complement fixation reaction was positive for influenza A. with a dilution of 1 : 256. The effusion disappeared within a month by corticotherapy.

2. *Cardiac Complications.*

The existence of cardiac complications in influenza is commonly admitted but their frequency is subject to discussion [3,4,5,6] and many published reports do not carry serologic diagnosis. We found one case of acute pericarditis and one case of acute myocarditis with influenzal etiology.

Case 1. At the height of the Asiatic influenza pandemic, an eleven year old girl was admitted with acute pericarditis. From the beginning of her influenzal attack she had complained of retrosternal pain and she remained subfebrile and asthenic. Twenty days after the onset of the disease, cardiomegaly was observed by radioscopy and she was hospitalized. The examination revealed pericardial friction rub and dull sounds. Fluoroscopy showed an enlarged heart, beating weakly, and the electrocardiogram showed that T waves were negative in all the precordial leads. There was no increase in the amount of antistreptococcal antibodies and the tuberculin skin reaction was negative. However, the reaction of complement fixation was positive for influenza A at a dilution of 1 : 128. The patient was treated with penicillin and prednisone for six weeks as a precautionary measure even though all signs of pericarditis had disappeared by the tenth day of treatment.

Case 2. Acute myocarditis was discovered in an 18 month old boy. During the winter, when his family was suffering from influenza, he developed a cold and became pale and irritable. His temperature rose to 38.5 C. On admission he had signs of bronchitis with dull sounds in both bases and an enlarged liver. Fluoroscopy showed a miliary post-hilar webbing in the lungs. A few hours after admission edema of the lung proved fatal. An autopsy revealed an enlarged heart without congenital anomalies and a bilateral pleural effusion. Complement fixation for influenza B, in the serum extracted, was positive with a dilution of 1 : 32. This reaction, coupled with the age of the child and clinical observations, affirmed the diagnosis of acute asystole due to influenza myocarditis.

We must therefore admit the possibility of acute influenzal pericarditis or myocarditis among patients who present pulmonay symptoms of influenza either during epidemics or in isolated incidents. When there is no epidemic to indicate the source of infection only a systematic serologic survey can determine its viral etiology.

3. *The Hematological Picture in Influenza.*

This subject has been thoroughly studied. As far as the red cell series is concerned its modifications are few and not characteristic. Observations of hemolytic anemias have been published. [7,8] It is usual to expect leukopenia and neutropenia in influenza. Actually we noted leukopenia (under 6,000) in only 17 per cent of our cases and neutropenia (under 40 per cent) in only 20 per cent. However, hyperleukocytosis (over 10,000) was present in 46 per cent of our cases and polynucleosis (over 60 per cent) also in 46 per cent. These latter were probably due to immaturity and to the frequency of microbial secondary infections.

Of great interest however were the two cases of benign influenzal reticulosis which we observed and of which we have seen no examples in medical literature.

Case 1. A six year old boy was admitted to the hospital at the height of the Asiatic influenza pandemic with a fever of 40 C. which had persisted since the night before. Neither splenomegaly nor lymphadenopathy were present but a surprisingly abnormal hemogram was noted:

3,500,000 red blood cells
40,000 white blood cells
Differential:

28	polymorphs
1	eosinophil
1	basophil
2	plasmacytes
52	lymphocytes
11	transitional monocytes
1	monocyte
4	erythroblasts

These anomalies were found again two days later. A bone marrow examination indicated severe monocytosis. The Paul-Bunnel test was negative. The fever persisted for 48 hours during which no particular treatment was given. On the seventeenth day after admission there were only 14,000 white blood cells of which 47 per cent were polynuclear. On the thirty-fourth day the hemogram was normal:

4,500,000 red blood cells
9,000 white blood cells
Differential:

61	polymorphs
1	eosinophil
20	lymphocytes
14	transitional monocytes
4	monocytes

Complement fixation tests were positive for influenza A with a dilution of 1 : 128 the first time and 1 : 32 a month later.

Case 2. In the second case a clinical syndrome of acute, benign lymphadenitis was noted. A six year old boy was hospitalized after three days of

fever. He displayed a peripheral micropolyadenopathy, severe splenomegaly (four fingerbreadths below the costal margin) and a right interbronchial ganglion, discovered on the thoracic radiogram. His hemogram was as follows:

3,000,000 red blood cells
14,000 white blood cells

Differential:	50	polymorphs
	15	lymphocytes
	16	transitional monocytes
	15	monocytes
	2	Türk cells
	2	plasmacytes

A bone marrow study showed plasmacytosis and eosinophilia. A lymph node biopsy revealed a typical form of benign reticulosis suggesting infectious mononucleosis. Paul-Bunnel test was negative as was the serologic test for toxoplasmosis. The skin reaction to tuberculin was positive but the child had received a BCG injection one year previously. However, the reaction of complement fixation was positive for influenza A with a dilution of 1 : 64 and fifteen days later, 1 : 16, accompanied by the appearance of cold hemagglutinins (1 : 40 then 1 : 20).

The child was treated with penicillin and prednisone. After fifteen days the hemogram was normal; after thirty days the splenomegaly and lymphadenopathy had disappeared.

These observations show that influenza can present a picture of reticulosis and can simulate acute benign lymphadenitis. In a case of apparent infectious mononucleosis with a negative Paul-Bunnel reaction it is advisable to look for an influenzal etiology.

4. Acute Influenzal Nephritis.

Attention has been drawn to this cause of nephritis during the last few years. During the pandemic of 1957, serologically confirmed cases were published by Ferrari [9] in Italy and Michon [10] in France.

Influenza must be suspected, during a period of epidemic, as the cause of nephritis when the nephritis occurs very soon after an infectious episode without tonsillitis or when it is associated with a viral type of pulmonary infection. Only laboratory investigation can confirm this etiology, on the one hand by offering a serological diagnosis of influenza, and on the other hand by excluding the responsibility of a secondary streptococcal infection. This can be done through bacteriological studies of the throat and immunological tests.

Case 1. An eleven year old boy was seen two weeks after an attack of influenza during the Asiatic flu pandemic. His urine was dark in color and upon examination we found proteinuria at 1 gram per day and microscopic hematuria.

A search for hemolytic streptococcus in the throat was negative and the liter of streptococcal antibodies was normal. However the complement fixation was positive for influenza A at a dilution of 1 : 32, twelve days later at 1 : 16. Taking into account the context of the epidemic, these rates were considered significant. This acute hemorrhagic glomerulo-nephritis had a long course and the microscopic hematuria and albuminuria did not disappear for two years.

Case 2. A boy of seven was seen 18 days after a severe case of influenza during the 1957 pandemic. It was discovered that he had nephritis with albuminuria (0.70 Gm. per day), microscopic hematuria, cylindruria and slight arterial hypertension of 120/80. Streptococcal etiology was discarded. Complement fixation was positive for influenza A with a dilution of 1 : 128 on November 28, 1 : 64 on December 13 and zero on February 3. The course of the illness in this case was rapidly favorable and the Addis count became normal in the third month.

According to Michon, these acute influenzal nephritides are characterized by the absence or brevity of the interval between the initial infection and the appearance of the renal symptoms. In our two cases, however, there was a free interval of 15 days. Moreover, our first case showed through its two year course that the recovery in acute influenzal nephritis is not always as rapid as Michon claims.

5. *Influenzal Hepatitis with Jaundice.*

In 1950 Chaptal [11] demonstrated serologically the existence of influenzal hepatitis with jaundice. During the Asiatic flu pandemic, Cantarutti and Panizon [12] observed at Padua five cases of hepatitis to which they were able to attribute an influenzal etiology through Hirst's reaction. Four of our patients had jaundice which, by clinical tests and the positive complement fixation reaction, we were able to trace back to influenza.

Case 1. A five year old girl seen 15 days after an attack of influenza presented a definite jaundice with discoloration of the feces and positive flocculation tests. CF was positive for virus A with a dilution of 1 : 64 and later of 1 : 128. Recovery was rapid.

Case 2. A girl of four presented, clinically and biologically, a mild infectious jaundice fifteen days after an attack of viral pneumonia. CF was at first negative, then positive for influenza A with a dilution of 1 : 16 on the twelfth day, 1 : 128 after fifteen days. The illness proved rapidly regressive.

Case 3. This was similar to cases 1 and 2. A three year old girl, two weeks after recovering from influenza with consolidation of the middle lobe and a pleural reaction, developed a mild, infectious jaundice which was rapidly regressive. CF was positive for influenza A with a dilution of 1 : 32, then 15 days later 1 : 16, 5 days later 0.

Case 4. This case, that of a 12 year old girl, differed from the others in that the illness began with jaundice. Since the jaundice appeared when the

Asiatic flu pandemic was at its height we searched for a possible influenzal etiology although the child had no symptoms of respiratory difficulties. CF was positive for influenza A with a dilution of 1 : 32, 10 days later 1 : 64.

In the absence of specific tests for epidemic hepatitis one can certainly discuss an association of the two viruses in these cases. It is more logical, however, to admit that the influenza virus is responsible for the hepatitis. Our last case suggests that influenza can present a picture of mild hepatitis without initial influenzal or respiratory symptoms.

6. Influenzal Encephalitis.

We shall only touch on this most complicated question. Although experimentally the influenza virus has displayed a certain neurotropic strength and although polio-encephalitis has been produced experimentally in monkeys [13] and in mice; [14] in human pathology the virus has only been isolated from cerebro-spinal fluid or from fragments of nerve tissue. [3,15] Moreover, the autopsies of patients who have died from nervous complications of serologically confirmed influenza, show that the lesions are not of an encephalitic nature but correspond to the cerebral disturbances of vascular or neurovegetative origin, such as seen in malignant syndromes of infectious diseases and in the cerebral manifestations of metabolic disturbances. [16,17] However, even if the concept of influenzal encephalitis in the strict sense of the term remains subject to discussion, the pandemic of 1957 has confirmed the frequency and diversity of the neurological complications of influenza. We have recorded two cases with such complications.

Case 1. The first was a seven year old boy. During an attack of influenza A serologically confirmed, (0, then positive with a dilution of 1 : 128 on the 12th day, 1 : 32 after 20 days, then again 0 after 2 months) coma had occured with high fever and convulsive pains on the right side. Clinically the symptoms suggested cerebral thrombosis and the child was treated with anti-coagulants with no success. He gradually came out of the coma but a paralysis of the right side persisted and finally he developed epileptic complications. Although one cannot exclude the possibility of cerebral vascular accident during influenza, it is probable that this was an influenzal encephalitis of the convulsive and hemiplegic form.

Case 2. Ten days after an attack of influenza a girl of five developed headaches, a slight meningeal rigidity and torpor. Her cerebro-spinal fluid contained 8 cells and 1 Gm. of albumin. This mild state of meningeal encephalitis disappeared within 15 days. CF proved its connection with influenza A, being positive with a dilution of 1 : 64, 10 days later with 1 : 128.

Summary

Thus it appears that influenza frequently affects parts of the body other than the respiratory tract. Without doubt these 13 out of 98 serologically confirmed influenza cases give an erroneous indication, erring heavily on the side of excess, of the actual frequency of extrarespiratory complications since most cases of simple influenza are not hospitalized. We can only assert that of the cases of influenza among children who were hospitalized, 13 per cent have presented unexpected complications.

In some of these 13 cases the clinical diagnosis was influenced by the existence of an epidemic (six cases during the Asiatic flu pandemic). In 8 cases there was a previous history of influenza with or without viral pneumonopathy. But in two cases, one with serofibrinous pleurisy and one with reticulosis, there was neither the epidemic nor the history of an attack of influenza to account for these complications.

Thus, even during non-epidemic periods and even without histories of recent attacks, it is well to think of influenza in illnesses as diverse as jaundice, myocarditis, pericarditis, acute nephritis or the syndrome of acute lymphadenitis. Confirmation of the diagnosis, however, must rest on two simultaneous actions: first a search for and elimination of any possible secondary infection or associated disease (tuberculosis in the case of pleurisy, streptococcal infection in the case of nephritis, infectious mononucleosis in the case of reticulosis, etc.) and, secondly, a rigorous insistence on a positive complement fixation test for influenza with truly significant titers.

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