Neurological Findings in HIV-Infected Children: A Review of 49 Cases

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ABSTRACT: Many HIV-infected children have neurological involvement. We present our observations in 49 cases, 58% of which had some form of clinical neurological impairment. Most of the patients affected (71%) presented with progressive encephalopathy, characterized by developmental delay with loss of acquisitions and cognitive decline, an impaired growth curve, microcephaly and corticospinal dysfunction. CT-scan imaging shows cerebral atrophy in all cases and basal ganglia calcifications in 29%. Non-specific abnormalities are found on the EEG in two-thirds of cases and in the CSF in slightly less than half the cases. Pathological studies sometime revealed HIV encephalitis or lateral corticospinal tracts degeneration. Neurological impairment secondary to vascular events, neoplasms or opportunistic infections were rare, especially when compared with the adult HIV population.

RÉSUMÉ: Atteinte neurologique chez les enfants infectés par le VIH : observations chez 49 patients. Un nombre important d'enfants infectés par le VIH développent des complications neurologiques. Nous rapportons nos observations chez 49 patients. 58% avaient une atteinte neurologique clinique. La plupart des enfants affectés (71%) présentaient un tableau d'encéphalopathie progressive, caractérisée par un retard de développement avec une perte des acquisitions et une atteinte des fonctions cognitives, un retard staturo-pondéral, une microcéphalie et une atteinte corticospinale. Le CT-scan a démontré une atrophie cérébrale dans tous les cas ainsi que des calcifications des noyaux gris centraux dans 29% des cas. Des anomalies non-spécifiques ont été notées à l'EEG dans deux tiers des cas et dans le LCR dans un peu moins de la moitié des cas. L'étude pathologique a parfois révèlé une encéphalite reliée au VIH et / ou une dégénerescence des faisceaux corticospinaux latéraux. Les troubles neurologiques secondaires aux atteintes vasculaires, aux néoplasies ou aux infections opportunistes demeurent nettement moins fréquents que dans la population VIH adulte.

Can. J. Neurol. Sci. 1992; 19: 453-457

Shortly after the first descriptions of AIDS cases in adults appeared in the scientific literature, reports have demonstrated a variety of clinical presentations in HIV-infected children.[1-3] A number of studies[4-8] subsequently showed a wide spectrum of neurological involvement, that differs markedly from that which is found in the adult HIV population.

Presented here are the observations in 49 patients treated at Sainte-Justine Hospital.

Patients

Observations in 49 consecutive patients, investigated at Sainte-Justine Hospital from 1981 to 1991, were studied in a retrospective fashion. These patients were followed, most of them since birth, by one of the authors (N.L.). Consultation in neurology was obtained for all patients who presented evidence of neurological involvement, and para-clinical investigations were performed when judged necessary. Autopsy was obtained whenever possible.

The majority developed symptomatic infection, defined as P2 class according to the classification for HIV-infected children under 13 years of age.[9] Nine patients had an asymptomatic infection (P1 class). No P0-class child was included in the study. One patient was born with great prematurity and died at three weeks of age. He was not included in the study and thus, 48 patients were retained in our review.

Results

Forty-eight patients were studied, 36 of whom were black (32 Haitians, two Africans, two Caribbeans), 11 were Caucasian and one was Vietnamese.

Forty-six of the 48 patients contracted the disease by maternal (vertical) transmission, while the remaining two were infected by blood transfusion at a time when routine screening of blood products for HIV was not yet instituted. Twenty-five of the 46 patients were females, 21 were males. The results are summarized in Table 1.

Clinical Manifestations

Twenty-eight (58%) of the 48 patients studied had symptomatic neurological impairment. Of these, 20 (71%) had

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Received January 21, 1992. Accepted in final form June 1, 1992.
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progressive encephalopathy, characterized by developmental delay with eventual loss of previous acquisitions, impaired growth and corticospinal tract dysfunction (see Table 2).

Most of the patients with progressive encephalopathy presented a sub-acute evolution with steady decline in cognitive and motor function. Five patients had an initial period of neuro-

Table 1. Summarized Results for all Patients (n = 48 Patients)

Patient	AIDS Classification	Age at Diagnosis (Months)	Age at Last Follow-up (Months)	Death	Neurological Involvement	Type
1	P2 A B D13	6	6	+	YES	PROGRESSIVE
2	P2 A B C D2	51	56	+	YES	PROGRESSIVE + SPINAL CORD
3	P2 A B D23	27	52	+	ASYMPTOM.	
4	P2 A B D13	10	13	+	YES	PROGRESSIVE
5	P2 A D13	7	8	+	ASYMPTOM.	
6	P2 A B D13	6	7	+	YES	PROGRESSIVE
7	P2 A B D123	8	32	+	YES	PROGRESSIVE
8	P2 A B D13	20	45	+	YES	PROGRESSIVE
9	P2 A C	38	38		NO	
10	P2 A B C D3	15	54	+	YES	PROGRESSIVE
11	P2 A B D3	8	98	+	YES	PROGRESSIVE + SPINAL CORD
12	P2 A F	22	56		NO	
13	P2 A B D13	48	72	+	YES	PROGRESSIVE
14	P2 A B D13	6	7	+	YES	UNCLASSIFIED
15	P2 A D1	4	4	+	YES	UNCLASSIFIED
16	P2 B D1 F	6	8	+	YES	PROGRESSIVE
17	P2 A B D13	24	30	+	YES	PROGRESSIVE
18	P2 A B D3 F	7	31	+	YES	PROGRESSIVE
19	P2 A C	49	96		NO	
20	P2 D123	37	52	+	YES	STATIC
21	P1 B	12	56		NO	
22	P2 A B C D123	10	42	+	YES	PROGRESSIVE
23	P1 B	10	70		NO	
24	P2 A B D23	6	19		YES	PROGRESSIVE
25	P2 A B C D12 F	16	46	+	YES	PROGRESSIVE
26	P2 A B F	15	35	+	YES	PROGRESSIVE
27	P2 A C	72	108		ASYMPTOM.	
28	P2 A C	9	37		YES	UNCLASSIFIED
29	P2 A B F	18	33	+	YES	PROGRESSIVE
30	P2 A B D13	3	8	+	YES	PROGRESSIVE
31	P2 A B D13	7	38	+	YES	PROGRESSIVE
32	P2 A F	86	126		ASYMPTOM.	
33	P2 A B D3 F	2	33		YES	PROGRESSIVE
34	P2 A	14	28		YES	STATIC
35	P2 A F	16	38		NO	
36	P2 A	29	36		NO	
37	P2 A D1	2	10		NO	
38	P1 B	14	14		NO	
39	P2 A F	27	32		NO	
40	P1 A	7	16		NO	
41	P1 B	3	15		ASYMPTOM.	
42	P2 A D1	2	15		NO	
43	P2 A D13	6	17	+	YES	STATIC
44	P1 B	1	7		ASYMPTOM.	
45	P2 D1	3	7		YES	UNCLASSIFIED
46	P2 D1	118	120		NO	
47	P2 F	59	63		NO	
48	P2 A B	21	23		YES	UNCLASSIFIED

age at diagnosis = age at diagnosis of HIV infection; yes = clinical impairment; asymptom. = para-clinical abnormalities; progressive = progressive encephalopathy; static = static encephalopathy; unclassified = definite neurological involvement but cannot be classified into progressive or static categories. See text for further discussion.

https://doi.org/10.1017/S0317167100041639 Published online by Cambridge University Press

logical stability (plateau) with subsequent deterioration. One patient had documented improvement with catch-up growth and cognitive development for four years, before deteriorating rapidly to a demential state. Another patient had catch-up motor development for nine months before an eventual deterioration.

Although variable, onset of neurological symptoms for most of these patients was in the first year of life. Seventeen of these 20 patients are deceased, at an average age of 33 months

Microcephaly was found in 55% of the 20 patients.

One patient presented initially with a clinical picture of transverse myelitis and developed signs of progressive encephalopathy 15 months later. Another patient, while suffering from progressive encephalopathy since the first year of life, presented at five years of age with clinical evidence of spinal cord dysfunction, documented by somatosensory evoked potentials.

None of the patients had movement disorder or signs of cerebellar dysfunction, nor was there any clinical evidence of peripheral involvement. Seizures were a rare feature, occurring in a non-febrile context in only two cases. Brain stem features were also infrequent (three cases) .

Among the 28 patients with neurological dysfunction, three could be classified as having static encephalopathy with varying degree of developmental delay and corticospinal dysfunction and a stable evolution over a one-year period or more. Five other patients could not be classified because of a short follow-up period (average four months) .

Of the initial cohort (n = 48), six patients had asymptomatic neurological involvement (see Table 3). Despite having no neurological signs or symptoms, five of the six patients had cerebral atrophy on CT. The remaining patient had microcephaly and an impaired growth curve. Interestingly, one nine-year-old child is asymptomatic despite having cerebral atrophy and basal ganglia calcifications on the CT.

The fourteen remaining patients were free of clinical and para-clinical involvement at an average age of 40 months.

The patients' neurological status are summarized in Table 3.

Table 2. Clinical Findings in Patients with Progressive Encephalopathy (n = 20 Patients)

Clinical Findings	% of Patients
Developmental delay (including loss of acquisitions and cognitive decline)	100
Impaired growth curve	94
Corticospinal tract dysfunction	85
Microcephaly	55
Brain stem symptoms	15
Spinal cord signs	10
Seizures	10

Table 3. Neurological Status in HIV-Infected Children (n = 48 Patients)

Definite (symptomatic) neurological impairment		28 (58%)
progressive encephalopathy	20	
static encephalopathy	3	
unclassified	5	
Possible (asymptomatic) neurological impairment (para-clinical abnormalities)		6 (13%)
Normal neurological findings		14 (29%)

One patient died of a massive ischemic stroke at four months of age. None of the patients developed neoplasms, nor was there any clinical or laboratory evidence of opportunistic infection. Two patients developed streptococcal meningitis.

Laboratory Results

Seventeen of the 20 patients with progressive encephalopathy had one or more CT scans. All of them had cerebral atrophy, cerebellar atrophy being a much less frequent feature. Five (29%) showed calcifications of the basal ganglia region. The three patients with static encephalopathy also had cerebral atrophy, but none had calcifications.

EEG was performed on nine of the 20 patients with progressive encephalopathy. Two-thirds were abnormal with non-specific diffuse slowing.

CSF studies revealed slightly increased protein (50-100 mg%) in five of 11 patients tested in the progressive encephalopathy group (see Table 4).

Pathological Findings

Ten of the twenty patients with progressive encephalopathy had an autopsy. Changes compatible with HIV-related encephalitis were found in four cases. These changes included inflammatory cell infiltrates, microglial nodules, and multinucleated giant cells (see Figure 1). These findings were also noted in a seven-month-old child not included in the progressive encephalopathy group because of early death. In another patient with progressive encephalopathy, histological studies showed signs of HIV leukoencephalopathy.

Degeneration of the lateral corticospinal tracts was noted in five of ten cases. Another case revealed a vacuolar pattern of

Table 4. Para-clinical Results in Patients with Progressive Encephalopathy

		% of Patients
CT-scan (17 patients)	cerebral atrophy	100
	basal ganglia Ca^{++}	29
EEG (9 patients)	diffuse slowing	67
CSF (11 patients)	increased proteinorrachia	45

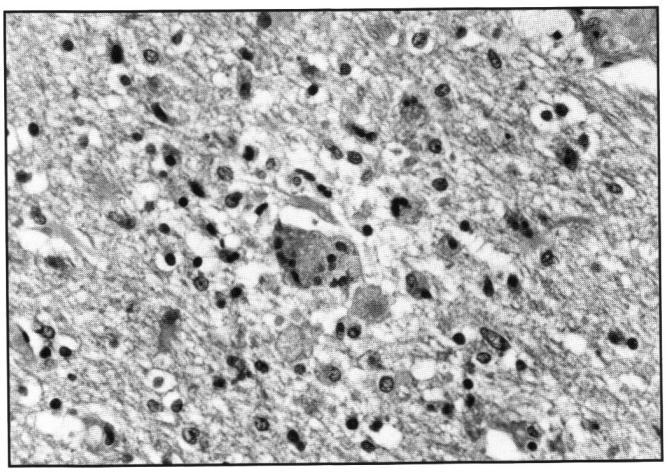

Figure 1 — HIV encephalitis: inflammatory focus with multinucleated giant cells, microglial cells and reactive gliosis in a 6-year-old HIV-infected child. Hematoxylin-phloxin-safran. 400x.

https://doi.org/10.1017/S0317167100041639 Published online by Cambridge University Press

degeneration of both the lateral corticospinal tracts and the posterior columns (see Figure 2).

Histological evidence of CMV encephalitis was observed in two cases, and Candida Albicans encephalitis in one.

Discussion

The presence and extent of neurological involvement in HIV-infected children varies as seen in the present day literature.[7,8,10] In their published series, Epstein et al.[7] found some form of neurological involvement in 57 of 79 HIV-infected children (72%), about 60% of which was of the progressive encephalopathy type, as previously described, the other 40% taking the form of a static encephalopathy. In her review, Belman[8] cites a 50 to 62% incidence of "progressive encephalopathy" in infants and children with symptomatic HIV infection.

In our study, 58% of HIV-infected children presented with clinical neurological impairment. We believe this figure probably represents an underestimate of the true incidence. The six cases classified as having asymptomatic neurological dysfunction are understandably at high risk of eventually developing neurological clinical signs or symptoms related to HIV infection. Furthermore, the patients considered free of neurological impairment did not have systematic CT-scanning or CSF analysis. In addition, three patients with asymptomatic neurological involvement and three of the 14 patients free of neurological dysfunction were less than 15 months of age at the time of this study. Although, as previously mentioned, most of the patients became symptomatic in the first year of life, there are a number of cases, both in our series and in the literature, of initial symptoms emerging later in infancy.[7,8,10]

However, other factors must be taken into account when discussing cerebral atrophy in HIV infected children, such as in-utero exposure to drugs.[11,12] Subsequent environmental conditions and educational stimuli have also been shown to be potential factors in developmental delay.[13]

A three to one ratio of progressive to static encephalopathy has been suggested.[8,10] Although we found 71% of progressive encephalopathy among the 28 patients with clinical impairment of the central nervous system, only three cases (11%) could be classified with certitude as static encephalopathy. Whether or not these two types of encephalopathy represent different pathophysiological processes remains unclear. It has been suggested that static encephalopathy is not the result of direct HIV infection of the brain but represents the effect of other deleterious in-utero and perinatal factors such as exposure to drugs, prematurity and other infections.[7]

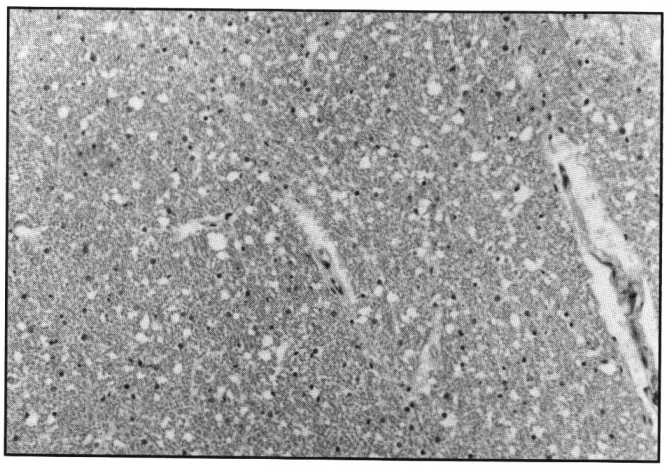

Figure 2 — Vacuolar myelopathy: mild spongiosis in the gracilis fasciculus in a 2-year-old HIV-infected child. Hematoxylin-phloxin-safran. 100x.

The main features of progressive encephalopathy are developmental delay, including language retardation, an impaired growth curve and a high rate of pyramidal dysfunction. Eventual severe cognitive decline and progression to a spastic quadriparetic state usually occurs, if systemic conditions allow a long enough period of survival.

No clear-cut cases of peripheral nerve involvement have been described in HIV-infected children. This differs markedly from the findings in the adult AIDS-population, in which at least 15% of patients are symptomatic of peripheral nervous system involvement, this figure reaching 60% in electrophysiological or histological studies.[14]

Brain atrophy on CT appears to be an almost universal finding in children with progressive encephalopathy.[4-6] Calcifications of the basal ganglia carry an ominous prognosis.[8] We have observed this finding in our series of patients, one notable exception being a 9-year-old asymptomatic child with cerebral atrophy and basal ganglia calcifications observed on CT.

We found a higher than expected rate of abnormal EEGs (67%) and increased CSF protein count (45%) in children with progressive encephalopathy although these changes were not specific.

Neoplasms of the central nervous system and particularly lymphoma have been recognized in HIV-infected children,[7,8,10] albeit at a much lower rate than in the adult HIV population where primary CNS lymphoma is found in 1-2% of patients.[15] No neoplasms were found in our patients. We expect however to see more of these complications as the patients become older. Presently, 20% of the 49 patients have reached five years of age. This represents 40% of the living patients.

Cerebrovascular complications have been described in children with HIV infection.[8,10] Ischemic infarcts occur, as do intracerebral hemorrhages, the latter mostly in the context of thrombocytopenia. Only one of our patients suffered a vascular event, a major ischemic stroke.

The most common pathological observations in our patients, HIV encephalitis and corticospinal tract degeneration, are in concordance with the usual findings in HIV infected children.[7,10,16,17] Vacuolar myelopathy is a frequently noted finding in the adult population, occurring in some 22% of patients in an autopsy series[18] but is seldomly found in the pediatric HIV population.[17]

Three pathologically documented cases of central nervous system opportunistic infections were observed (two CMV cases, one Candida Albicans case). Though much less frequent than in the adult HIV population, neurological opportunistic infections do occur in HIV-infected children.[7,8] The association of HIV and CMV is well known, both in neurological and systemic infections. Candida Albicans and toxoplasmosis infections have been reported before,[7,8] although the latter is generally a congenital condition, acquired infections being rare.[19]

By comparison, the clinical picture of HIV-infection in adults is dominated by opportunistic infections, the most frequent

https://doi.org/10.1017/S0317167100041639 Published online by Cambridge University Press

being cerebral toxoplasma, occurring in some 25-30% of patients.[15] Other frequently encountered pathogens in adults include Cryptococcus neoformans, the JC virus (progressive multifocal encephalopathy) and viruses of the Herpes family.

Conclusions

The results of this series are generally in concordance with current data on neurological impairment in children with HIV infection. The percentage of central nervous system involvement is high and the majority of those affected present with a progressive encephalopathy. Cognitive development and growth are frequently further impaired by concommitant systemic diseases.

Unfortunately, the incidence of HIV infection in children continues to increase and the prognosis remains somber. More research is needed to help elucidate the pathophysiology implicated in the different sub-types of encephalopathy. A multidisciplinary approach is obviously of critical importance in the investigation of this complex disease state.

References

1. Joncas JH, Delage G, Chad Z, et al. Acquired or congenital immunodeficiency syndrome in infants born of Haitian mothers. N Engl J Med 1983; 308: 842.
2. Oleske J, Minnefor A, Cooper R, et al. Immune deficiency syndrome in children. JAMA 1983; 249: 2345-2349.
3. Scott GB, Buck BE, Letermen JG, et al. Acquired immunodeficiency syndrome in infants. N Engl J Med 1984; 310: 76-81.
4. Epstein LG, Sharer LR, Joschi VV, et al. Progressive encephalopathy in children with acquired immunodeficiency syndrome. Ann Neurol 1985; 17: 488-496.
5. Belman AL, Ultman MH, Horoupian D. Neurological complications in infants and children with acquired immunodeficiency syndrome. Ann Neurol 1985; 18: 560-566.
6. Epstein LG, Sharer LR, Oleske JM. Neurological manifestations of human immunodeficiency virus in children. Pediatrics 1986; 78: 678-687.
7. Epstein LG, Sharer LR, Goudsmit J. Neurological and neuropathological features of human immunodeficiency virus infection in children. Ann Neurol 1988; 23(Suppl.): S19-S23.
8. Belman AL. AIDS and pediatric neurology. Neurol Clin 1990; 8: 571-603.
9. Morbidity and Mortality Weekly Report 1987; 36: 91-96.
10. Brouwers P, Belman AL, Epstein LG. Central nervous system involvement: manifestations and evaluation. *In*: Pizzo PA, Wilfert, CM, eds. Pediatric AIDS. The Challenge of HIV Infection in Infants, Children, And Adolescents. Baltimore: Williams and Wilkins 1991; 318-335.
11. Naeye RL, Blanc W, Leblanc W, et al. Fetal complications of maternal heroin addiction: abnormal growth, infections, and episodes of stress. J Pediatrics 1973; 83: 1055-1061.
12. Day NL, Jasperse D, Richardson G, et al. Prenatal exposure to alcohol: effect on infant growth and morphological characteristics. Pediatrics 1989; 84: 536-541.
13. Capron C, Duyme M. Assessment of effects of socio-economic status on IQ in a full cross-effecting study. Nature 1989; 340: 552-554.
14. Katirjy MB. Peripheral nervous system manifestations of human immunodeficiency virus infection. *In*: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, eds. Neurology in Clinical Practice. Butterworth-Heinemann 1991; 1107-1111.
15. Tucker T. Central nervous system manifestations of human immunodeficiency virus infection. *In*: Bradley WG, Daroff RB, Fenichel , Marsden CD, eds. Neurology in Clinical Practice. Butterworth-Heinemann 1991; 1098-1106.
16. Budka H, Wiley CA, Kleihues P. HIV-associated disease of the nervous system: review of nomenclature and proposal for neuropathology-based terminology. Brain Pathology 1991; 1: 143-152.
17. Dickson DW, Belman AL, Kim TS, et al. Spinal cord pathology in pediatric acquired immunodeficiency syndrome. Neurology 1989; 39: 227-235.
18. Petito CK, Navia BA, Cho E-S, et al. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. N Engl J Med. 1985; 312: 874-879.
19. Shanks GD, Redfield RR, Fischer GW. Toxoplasma encephalitis in an infant with acquired immunodeficiency syndrome. Ped Inf Dis Journal 1987; 6: 70-71.

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