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HIV-1–related encephalopathy in infants compared with children and adults

[Articles]

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Outline

Abstract

Objective: To characterize the specificities of HIV-1–related encephalopathy in children.

Methods: Comparison of patients from the French Perinatal Cohort of children born to HIV-1–infected mothers and followed from birth with the French SEROCO Cohort of adults with a known date of infection. Our study examines 1) the characteristics of encephalopathy with onset before 1 year, after 1 year, and in adults, and 2) the maternal and birth characteristics of infants who developed AIDS before 1 year and went on to develop either encephalopathy or opportunistic infection.

Results: The incidence of encephalopathy was higher in children than in adults during the first year (9.9% versus 0.3%) and intermediate during the second year (4.2% versus 0%) after infection but was similar thereafter (less than 1% per year in each group). The resulting cumulative incidence at 7 years postinfection reached 16% in children and 5% in adults. Encephalopathy that developed before 1 year 1) was more frequently an isolated symptom of AIDS, 2) was associated with a reduction of intrauterine brain growth, 3) was associated with a very low level of HIV-1 RNA in CSF, 4) occurred at a higher level of immunocompetence after taking into account the decrease in CD4 lymphocytes with age, and 5) was not prevented by zidovudine treatment during gestation.

Conclusions: Early encephalopathy in infants has a different pathophysiologic mechanism than that occurring in children, which in turn shows similarities with that observed in adults. Early encephalopathy is probably related to the occurrence of pathologic events during late fetal life.

Development of an encephalopathy is one of the most severe complications of AIDS but its frequency at different ages has long been disputed. During the early years of the epidemic, HIV-related encephalopathy, among other AIDS-defining symptoms, was considered much more frequent in pediatric patients than in adults. However, in two very large cohorts, the progression to AIDS-defining symptoms in children was estimated at 19% during the first year of life but at 4.5% per year thereafter, indicating that the higher risk of progression was maximum during the first year. [1,2] There was also a clinical impression that, in children, HIV-1–related encephalopathy differed from other AIDS-defining symptoms in terms of individual prognosis and might correspond to different viral and immunologic conditions. This led to the hypothesis that neurologic symptoms in HIV-1–infected children that occur early (during the first 1 or 2 years of life) might be of different significance than those occurring later in children, which in turn might have characteristics close to those of HIV-1–related encephalopathy in adults. HIV-1 encephalopathy in very young children could be a very specific consequence of the interaction between HIV-1 and the developing nervous system and might require a specific therapeutic approach.

To evaluate this hypothesis, we initially examined the occurrence of encephalopathy in two well established and conjointly designed cohorts of HIV-1–infected patients: the French Perinatal Cohort and the French SEROCO Cohort of adult patients with a known date of HIV-1 infection. We subsequently evaluated the clinical and biologic characteristics of children whose encephalopathy had an onset before 1 year and compared them with those of children with later occurring encephalopathy and with those of adults. Finally, among children who developed AIDS before 1 year, we compared the maternal and birth characteristics of infants who went on to develop encephalopathy with those of infants who went on to develop opportunistic infection.

Studied population and methods.

Design of the pediatric cohort.

The French Perinatal HIV Cohort involves a network of 100 obstetric and pediatric centers throughout France and its design and operation have been extensively described in previous publications. [3] Mother-child pairs are enrolled if the mother's HIV seropositivity is known at delivery at the latest, and after the informed consent of parents. The centers undertake to enroll all mother-child pairs except in cases of parental refusal (the number of which is noted in each center). The participating centers forward to a central coordinator (INSERM U292) all clinical and laboratory findings in infants born to HIV-1–seropositive mothers. The data are collected every 3 months from birth to 18 months, then every 6 months, and transmitted anonymously. Among 3,364 mother-child pairs enrolled between late 1985 and December 1996, all HIV-1–infected infants (n = 426) were included in the current study. The general characteristics of the mothers have been described previously. [3] Zidovudine (AZT) treatment with protocol ACTG076 during pregnancy, at birth, and during the first weeks of neonatal life was proposed to all mothers included since May 1994 and given to 90% of them. The protocol, compliance, and results on risk of transmission on the same population have previously been described. [4] Most of the children (73%) received AZT at the onset of first symptom and 32% had combined therapy (without antiprotease in this study ending in 1996) during the most recent years of the study.

Definition of HIV-1 infection in infants.

A child was considered infected if HIV-1 antibodies persisted beyond 18 months, or in case of death from HIV-1–related disease before this age, and considered uninfected if at least two HIV-1 antibody

tests were negative by the age of 18 months. Testing for HIV-1 antibodies was carried out with two commercial enzyme-linked immunosorbent assays (ELISA), and positive results confirmed by immunoblot. Immunoblot was considered negative when no antibody directed against the HIV-1 envelope glycoproteins was detected. For infants between 3 months and 18 months of age, infection status was determined using DNA-PCR and/or HIV-1 virus culture, performed in quality-controlled laboratories, according to previously reported consensus definitions. [5,6] The child was considered infected when two different samples tested concordantly positive, and was considered uninfected when no sample was positive and two different samples tested concordantly negative, at least one of which was at or beyond 3 months of age.

Evaluation of AIDS-defining events and severe immunodeficiency in children.

The diagnosis of AIDS-defining events and the definition of severe immunologic suppression was based on the 1994 Centers for Disease Control and Prevention (CDC) classification as follows.

Encephalopathy.

Encephalopathy was defined as a failure to attain or loss of developmental milestones or loss of intellectual ability, impaired brain growth, or an acquired microcephaly and an acquired symmetric motor deficit. However, the CDC criteria were clearly designed for infants. In the current study, encephalopathy was defined by the three clinical criteria for infants (first symptoms before 2 years); for children whose neurologic symptoms had an onset after 2 years, the criteria of acquired microcephaly was not required for diagnosis. The diagnosis was made by a pediatrician or a neuropediatrician in each center and all reports from centers were reviewed by a single neuropediatrician (M.T.). The center was directly contacted each time the report was incomplete.

Opportunistic infections.

The report of an opportunistic infection by participating centers was checked on the trimestrial reports and the validity of the diagnosis re-evaluated by a single immunologist. The initial opportunistic infection was due to Pneumocystis carinii pneumonia or cytomegalovirus in most of the patients.

Severe immunologic suppression.

The immunologic classification is based on CD4 lymphocyte counts or percentages. To be included in the category “severe immunologic suppression,” patients had either a CD4% of less than 15% regardless of the age of the infant, or a CD4 cell count <750 before age 1 year, <500 between 1 and 5 years, or <200 after that age.

CSF was examined in the 23 most recently followed children with neurologic symptoms. This was part of a protocol to obtain a viral quantification before the onset of new combinations of antiviral agents. Among these 23 patients, results obtained in the 19 patients who had CSF collection less than 3 months after the onset of the neurologic symptoms are reported in the current study.

Design of the adult cohort.

As of June 1996, the ongoing French multicenter SEROCO Cohort comprised 1,516 HIV-1–infected nonhemophiliac adults enrolled since 1988 in 17 participating centers (16 hospitals and a network of private practitioners). Patients receive thorough clinical and laboratory examinations at inclusion and are then seen every 6 or 3 months according to their clinical status. CD4 lymphocyte counts are determined at each visit by means of flow cytometry. All AIDS-defining illnesses (1993 European definition) are

checked on the basis of the participating center's files. 7 Eligible patients are those with a known date of seroconversion included in the cohort within 24 months after infection and with complete follow-up until death or June 1996 (n = 319). HIV seroconversion is documented by an interval of less than 24 months between a negative and a positive HIV antibody test, or an incomplete followed by a complete Western blot. The date of infection is defined as the date of primary symptomatic infection minus 15 days, or the date of the initial incomplete Western blot minus 1 month, or the midpoint between the two negative and positive HIV antibody tests minus 15 days, the median seroconversion interval being 7.0 months. The median time between infection and enrollment is 8.6 months.

HIV-1–related encephalopathy was prospectively diagnosed by a neurologist in each center. All reports were reviewed retrospectively by a neurologist on the basis of evocative clinical signs, radiologic examinations (including MRI), treatment of associated conditions, and response to specific treatment. The two cohorts (French Perinatal Cohort and French SEROCO Cohort) were designed together at the same time in the same institution (INSERM U 292).

Statistical analysis.

Proportions were compared using the $[chi]^2$ test or Fisher's exact test for expected values below 5. Quantitative variables were expressed as means ± 1 SD. They were compared by using the Student's t-test or the nonparametric Wilcoxon test. The Kaplan-Meier method was used to establish life table curves. They were compared with a log-rank test. The analysis was performed with SAS software (SAS Institute, Cary, NC).

Results.

Cumulative incidence of encephalopathy in HIV-1–infected infants and children.

Figure 1A shows the cumulative incidence of encephalopathy from birth in the 426 HIV-1–infected children out of the 3,364 children included in the French Pediatric Cohort during a median follow-up of 48 months (range 0 to 137). The cumulative incidence was 9.9% at 12 months and 13.1% at 24 months, whereas new cases steadily accumulated to reach a cumulative incidence of 16.3% at 84 months. To assess a potential preventive effect of a short course of AZT treatment on the occurrence of encephalopathy, we compared children who had been treated with AZT in utero and after birth according to protocol ACTG076 4 with children who had not undergone such treatment, most of whom were born before the onset of the protocol (figure 1B). The cumulative incidence of HIV-1 encephalopathy was similar in the two groups of patients ($p < 0.24$).

Graphic
[Help with image viewing]

Figure 1. (A) Cumulative incidence of HIV-related encephalopathy in HIV-1–infected children (solid line) and adults (dotted line) after birth or date of infection. (B) Incidence of HIV-related encephalopathy in children whose mothers were treated (solid line) or not treated (dotted line) with zidovudine (AZT) according to protocol ACTG076 (log rank:$p < 0.24$).

The relationship between progression to encephalopathy and the tested maternal or infant characteristics at birth was assessed by log-rank tests. As expected, 8-12 the risk of occurrence of an encephalopathy was dependent on the level of circulating CD4 lymphocyte numbers ($p < 0.002$) and detection of p24

antigen ($p < 0.05$) in the mother, and on the percentages of circulating CD4 lymphocytes ($p < 0.02$) and detection of p24 antigen ($p < 0.05$) in the infant. It did not depend on either the mode of acquisition of HIV-1 infection in the mother or her geographic origin. The progression to encephalopathy also appeared to be related to the detection at birth of adenopathy, spleen or liver enlargement ($p < 0.09$), or reduced weight ($p < 0.06$), although in these cases the significance level was not reached.

Comparison of early and later occurring encephalopathies in children.

The most rapid increase in the curve of the cumulative incidence of encephalopathy in children was from birth to 12 months of age. Therefore, we tested the hypothesis that progression to encephalopathy might be associated with different characteristics when the first symptoms are observed before (39 children in our study) or after 12 months of age (19 children).

Differences were observed both at birth and at time of encephalopathy. At birth, the head circumference (33 cm versus 34 cm;$p < 0.03$) and body weight (2,789 g versus 3,112 g;$p < 0.06$) were slightly lower in children with subsequent early onset encephalopathy, whereas circulating CD4 lymphocyte and p24 antigen levels in mother and child did not differ. The observed difference for head circumference was not related to a greater percentage of girls in children with subsequent early onset encephalopathy (58% versus 67%, early versus late). The same was true for the percentage of premature infants, which was similar in both groups (14 versus 18%). At time of onset of encephalopathy, neurologic symptoms and immunologic characteristics differed. Patients with encephalopathy before 12 months of age initially had a spastic paraparesis with cognitive impairment and, in some cases, buccolingual dyspraxia, whereas older patients expressed initially isolated paraparesis or acute psychosis or rapid mental deterioration, sometimes associated with parkinsonian symptoms without other motor deficits (reviewed in reference 13). Immunologically, patients whith onset of encephalopathy before the age of 1 year had more circulating CD4 lymphocytes (mean numbers: 1,190 versus 275 cells/μL, $p < 0.003$; mean percentages: 23% versus 12%, $p < 0.007$; patients with early versus late onset). This difference remained unchanged after taking into account the decrease in CD4 lymphocyte number and percentage with age (data not shown). 14 This suggests that early encephalopathy does not occur at the same level of immunodeficiency as later occurring encephalopathy.

Finally, the encephalopathy was frequently (56%) an isolated AIDS-defining symptom when its onset occurred before 1 year. The median survival time after onset of symptoms was 14 months in patients with both early and late onset encephalopathy, although the studied population was treated mainly by AZT alone.

Comparison of children with early encephalopathy or early opportunistic infection.

Early encephalopathy is associated with a reduction of prenatal brain growth.

Another way to evaluate the characteristics of early occurring encephalopathy was to compare infants who developed encephalopathy during the first year of life with infants who developed an opportunistic infection, the other most frequent AIDS-defining symptom during the same period of time. We restricted the study to infants with either one of the two events and excluded patients who had the two symptoms in association.

During the first year of life, 65 of the 426 included children developed an AIDS-defining illness, i.e., entered CDC category C. The initial AIDS-defining symptom was encephalopathy in 30 children, opportunistic infection in 28, recurrent bacterial infection in 2, and other isolated symptoms or

association of symptoms in 5. Altogether, an encephalopathy was observed in 39 children and an opportunistic infection in 36 children within the first 12 months. These two symptoms remained isolated in 26 (encephalopathy) and 23 (opportunistic infection) children and were associated in the same child in 13 patients.

At birth, the head circumference of newborns who developed an encephalopathy during the first year of life was lower than that of infants who developed an opportunistic infection (33 cm versus 34 cm, $p < 0.02$). The same was true for weight (2,753 g versus 3,180 g, $p < 0.02$). All other characteristics, including immunologic and virologic results, were similar. The results remained unchanged after adjustment for sex and prematurity (data not shown). This prenatal reduction of growth, including that of brain, was not a consequence of impaired maternal health status at birth, as the studied maternal characteristics were similar in both groups. The only difference strengthens the results: the mothers of infants with encephalopathy had a less severe disease than the mothers of infants with opportunistic infections, as they were less frequently in CDC class IV (14 versus 36%, $p < 0.10$).

Immunologic suppression and survival.

During early life, the comparison of the cumulative incidence of severe immunologic suppression revealed that it occurred earlier in patients who developed encephalopathy than in those who developed an opportunistic infection (figure 2). Finally, the survival curves after encephalopathy and after opportunistic infection showed a very different pattern. The cumulative survival rate decreased regularly, reaching 20% at 3 years after encephalopathy. After opportunistic infection, survival dropped to 60% after 2 months and remained stable until 3 years.

Graphic
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Figure 2. Incidence of severe immunologic suppression among children who developed an HIV-1–related encephalopathy (solid line) or an opportunistic infection (dotted line) before 1 year of age (log rank:$p < 0.002$).

Early encephalopathy is associated with a low level of HIV-1 RNA in CSF.

To better evaluate the respective pathophysiology of early and later occurring encephalopathy in children, we quantified viral RNA in the CSF of the 19 most recent patients, tested within 3 months of onset of neurologic symptoms. HIV-1 RNA levels were below the detection threshold in the CSF of 6 of 9 patients with early encephalopathy (onset before 1 year) and low (3 log RNA copies) in the 3 others, whereas they were uniformly high (mean ± SD: 3.9 ± 1.1 log RNA copies) in the CSF of 10 of 10 patients with encephalopathy of later onset. In contrast, HIV-1 RNA levels in the plasma of the same two groups of patients were identically high (mean ± SD: 4.8 ± 0.9 versus 5.1 ± 0.9; early versus late onset, $p = 0.1$).

Cumulative incidence from time of infection and characteristics of encephalopathy in adults.

Figure 1A shows the cumulative incidence of encephalopathy from time of infection in the 319 HIV-1–infected adults included in the SEROCO cohort during a median follow-up after infection of 82.0 months (range 0.4 to 119). The first case in adults was observed 9 months after infection and the remaining 10 cases occurred after 48 months. The cumulative incidence of encephalopathy reached 5% at 84 months. At time of diagnosis, the median circulating CD4 lymphocyte count was 30 cells/µL. The CD4 lymphocyte count was above 100 (264 cells/µL) in only one patient. Finally, in 4 of 11 patients,

encephalopathy occurred as the first AIDS-defining illness and remained isolated in one of them. The median survival after onset of encephalopathy was 3 months.

Discussion.

The frequency of encephalopathy in children infected with HIV-1 after mother-to-child transmission has been debated and is still commonly believed to be much higher than the frequency in adult patients. We observed that the incidence of encephalopathy was higher in children than in adults only during the first year (9.9% versus 0.3%) and to a lesser degree during the second year (4.2% versus 0%) after infection but was similar thereafter (less than 1% per year in each group). The resulting cumulative incidence at 7 years postinfection reached 16% in children and 5% in adults.

The two cohorts compared in this study were designed in parallel with the same protocol by the same team. In the pediatric cohort, one of the largest published so far, the rate of accumulation of encephalopathy was of the same order as in previously published cohorts of similar design. [15,16] Conversely, in adults, no results on patients with a known date of seroconversion have been published, to our knowledge. However, several studies have established the cumulative incidence of encephalopathy after the onset of severe immune deficiency. [17-19] The rate of accumulation of encephalopathy after onset of AIDS in the SEROCO cohort was in the same range as previously reported. [18]

It was hypothesized that early encephalopathy in children has a different pathophysiologic mechanism than the later occurring encephalopathy, which might present similarities to that observed in adults. Three main comparisons can be made through our study of HIV-1 encephalopathies occurring at different ages. First, encephalopathy was more frequently an isolated symptoms of AIDS when it occurred before 1 year (56% of patients with early AIDS) than later (32% of older children and 9% of adults). This frequent occurrence of encephalopathy in isolation in young HIV-1–infected children was also observed by Lobato et al. and Cooper et al. [15,16] Secondly, the level of immunocompetence was higher at onset of encephalopathy when this event occurred in the first year than later on, even after taking into account the decrease in CD4 lymphocytes with age. [14] Finally, survival after onset of encephalopathy was identical in infants and children but was poorer in adults, a results that needs to be reappraised after the introduction of the new potent combinations of antiviral drugs.

Our results support the view that early encephalopathy might be related to the occurrence of pathologic events during late fetal life. In very stringent conditions of comparison that were not used in previous studies testing head circumference at birth, we observed that infants who went on to develop encephalopathy already differed at birth from those who went on to develop an opportunistic infection during their first year of life; their head circumference and weight were already significantly lower. This was due neither to a higher proportion of girls or premature infants nor to the medical status of the mother, and suggests that brain growth was reduced during gestation of children with early occurring encephalopathy. Because head circumference at birth was also smaller in patients who developed early as compared with later onset encephalopathy, the reduction of intrauterine brain growth seems to be specifically related to early encephalopathy.

Several results have suggested that in HIV-1–infected infants with rapid progression, a viral infection occurred in utero [20,21] during the last weeks of pregnancy, which is also the period of fastest brain growth. An initial pathophysiologic hypothesis would be that early encephalopathy might be the consequence of a prenatal HIV-1 infection of the brain inducing a reduction of brain cell proliferation

during late pregnancy. HIV-1 infection of brain macrophages has been observed in neuropathologic studies of very young infants (including a 2-month-old baby; unpublished personal data, 1994) and their prenatal infection might limit the rate of proliferation of nearby astrocytes. Moreover, an accumulation of the HIV-1 nef protein has been described in astrocytes from brains of children with early encephalopathy (discussed in reference 22). The presence of viral proteins in developing astrocytes might also limit their proliferation during late pregnancy. Conversely, several findings suggest that early encephalopathy might be dependent on other factors, including: 1) the absence of protection against encephalopathy by AZT given during late pregnancy, as observed here and in two recently published studies, 23,24 a treatment that otherwise limits the rate of HIV-1 transmission by two-thirds, including in the same French Perinatal Cohort 4,24,25; 2) the published observations of an absence of p24 antigen-expressing cells in the brain of severely affected children 26; and 3) the current observation that CSF viral loads are very low in young children with severe encephalopathy whereas viral burden in plasma is elevated, which is not observed later on (see this work and reference 27). Our study found no evidence of a relationship with in utero exposure to illicit drugs, severity of maternal illness during pregnancy, or rate of prematurity. Other possibilities exist, including a coexisting viral infection of the fetus. Similarly, it has recently been demonstrated that infants with early but postnatal cytomegalovirus infection had a more rapid progression of HIV-1 disease and a higher risk of progressive neurologic disease. 28 The therapeutic strategy to prevent early encephalopathy in children has not yet been established but will probably require implementation during the late stages of pregnancy.

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Appendix

List of participants (for this analysis)

The following persons participated in the French Pediatric Cohort Study: Aix-en-Provence—E. Lagier, P. Opimel, B. Tadrist, D. Thevenieau, D. Tramier; Amiens—J.C. Boulanger, J. Gondry, B. Pautard, C. Roussel, C. Vergne; Angers—C. Binelli, J.M. Chennebault, P. Grosieux, C. Payant; Argenteuil—M. Piquet, N. Tordjeman; Aubervilliers—M.A. Rozan; Basse-Terre—B. Couchy, G. Sibille, S. Elmrabt; Bastia—P. Bastien, D. Colombani, O. Pincemaille, A. Salvetti, R. Turquini; Bayonne—C. Chabanier, P. Guerre, X. Hernandorena; Besançon—A. Bassignot, M. Bettinger, J. Leroy, J.P. Schaal; Blanc-Mesnil—A. Bajer, P. Balde; Bobigny—P. Deny; Bondy—A. Carbillon, P. Dauvergne, P. Faucher, E. Lachassinne, M. Uzan-Cohen; Bordeaux—M. Dallay, M. Denviou, D. Douard, H. Fleury, F. Guyon, C. Hocke, J. Horovitz, J.J. Leng, B. Masklier, D. Roux; Boulogne-Billancourt—I. Gilles; Bourg-La-Reine—A. Gantzer; Bullion—A.M. Colin-Gorki; Caen—P. Barjot, J. Brouard, F. Freymuth, G. Muller, J. Petit; Cayenne—C. Magnien, G. Patient, L. Stien; Clamart—F. Audibert, M. Dommergues, R. Frydman, L. Keros, Y. Ville; Clichy—M. Levardon, D. Sitbon; Colombes—C. Crenn-Hebert, P. Engelmann, C. Floch-Tudal, D. Saint-Léger; Corbeil-Essonnes—A. Blasquez, C. Daveau, A. Devidas, N. Lotfy; Courbevoie—P. Botto, P. Bourdon; Creil—P. Cesbron, G. Devulder, M. Duval-Arnould; Créteil—C. Huraux-Rendu, J.B. Paniel, C. Touboul, L. Desforges; Dijon—C. Kohli, I. Reynaud, T. Rousseau, P. Sagot; Dourdan—P. Guth, M. Lanza; Drancy—M. Boddaert; Dreux—M.F. Denavit, J. Garnier, Roudiere, S. Tribalat; Elbeuf—K. Lahsinat, M. Paquet, P. Pia; Evreux—C. Allouche, S. Elhaik; Evry—F. Grall, A. May, R. Nguyen; Fontainebleau—M.C. Dallot, P. Kalengi, P. Lhuillier; Fort-de-France—W. Cecile, R. Mezin, S. Sainte-Rose; Gonesse—A. Bech, G. Dauptain, J.B. Lobut; Ivry-sur-Seine—P. Pathier; Lagny-sur-Marne—G. Algava, A. Chalvon Dermesay, F. Pfeiffer; Le Chesnay—R. Busuttil, M. Harzic, M.C. Jacquemot, P. Lasfargues, F. Messaoudi, Teboul; Le Kremlin-Bicêtre—B. Bader-Meunier, S. Fridman; Le Lamentin—C. Chout, M. Monlouis; Lille—L.

Bocket, X. Codaccioni, S. Delmas, F. Mazingue, S. Vanderstichele; Limoges—J. Alain, F. Denis, S. Rogez, J.L. Tabaste, C. Venot; Longjumeau—A. Abbara, P. Bailly Salin, R. Bronstein, S. Dalvilic, H. Seaume; Lyon—A. Guichard, D. Raudrant, Y. Bertrand, J. Ritter, M. Tardy; Mantes-La-Jolie—J.C. Berardi, De Lanete, P. Grise, P. Wipff; Marseille—P. Botte, M. Gamerre, B. Guidicelli, S. Olivier, H. Ruf, C. Chau, B. Blanc, L. Cravello, P. Deboisse, M. Leclaire, G. Michel, D. Pelloux, C. Tamalet; Meaux—C. Crumiere, M.C. Demachy, V. Lefevre, F. Michel, B. Morel; Melun—Kleitz, B. Le Lorier, I. Pauly; Meulan—A. Robichez, D. Seguy; Montfermeil—F. Rideau, J.C. Ropert, P. Talon; Montpellier—B. Segondy, P. Benos, P. Boulot, Bouzinger, H. Dechaud, F. Laffargue, J. Nicolas, H. Vendrel; Montreuil—B. Heller-Roussin, S. Saint-Leger; Nancy—M.O. Delaporte, C. Hubert, M. Schweitzer; Nanterre—B. De Sarcus; Nantes—M. Auger, S. Billaudel, G. Boog, V. Ferre, F. Mechinaud, Winner; Neuilly-sur-Seine—D. Berterottiere, H. Boto; Nice—J. Cottalorda, A. Couderc, A. Deville, J. Allione, A. Bongain, J.Y. Gillet, F. Monpoux; Nimes—M.J. Carles, J. Dendale, C. Ferrer; Orléans—M. Barthez, D. Bondeux, L. Mesnard, M. Tescher; Orsay—C. De Gennes, P. Devianne, M.C. Razon; Perpignan—G. Bachelard, B. Bachelard, A. Roudil; Pointe-à-Pitre—M. Strobel; Poissy—I. Nisand, P. Pavard, M.C. Rousset; Pontoise—G. Mouchnino, P. Muray; Reims—D. Ingrand, M. Munzer, C. Quereux, D. Saniez; Rouen—V. Brossard, C. Buffet-Janvresse, B. Clavier, Duval, L. Marpeau; Saint-Etienne—A. Fresard, B. Pozzetto, M.N. Varlet; Saint-Denis—D. Ekoukou, Luzolo André, M.C. Allemon, V. Normand, M.P. Poupard, J.M. Retbi, D. Rotten, Seffert; Saint-Germain-en-Laye—B. Guyot, Michelon, P. Narcy; Saint-Martin—F. Bardinet, F. De Caunes; Saint-Maurice—R. Jeny, Robin; Sèvres—J. Belaisch-Allart, L. Segard; Suresnes—Colau, L. Savey; Toulouse—A. Berrebi, M. Cohen, P. De Coster, I. Lecuyer, A. Pontonnier, J. Puel, J. Tricoire; Tours—J.C. Borderon, F. Barin, A. Fignon, Lansac; La Trinité—N. Hugon; Vandoeuvre-Les-Nancy—Finance, Le Faou; Villejuif—E. Dussaix; Villeneuve-Saint-Georges—F. Guillot, B. Maria, F. Stampf, P. Tran Van; Villepinte—M.C. Boulanger, A. Broyard, P. Caubel, Y. Chitrit, M. Le Pennec; Vitry-sur-Seine—A. Lacroix-Coutry, G. Sturbois.

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