Multimodal Outcome at 7 Years of Age after Neonatal Arterial Ischemic Stroke

Stéphane Chabrier, MD[1,2], Emeline Peyric, MSc[1], Laure Drutel, MSc[1], Johanna Deron, MSc[1], Manoëlle Kossorotoff, MD, PhD[3,4], Mickaël Dinomais, MD, PhD[5,6], Leila Lazaro, MD[7], Jérémie Lefranc, MD[8], Guillaume Thébault, MSc[2,9], Gérard Dray, PhD[10], Joel Fluss, MD[11], Cyrille Renaud, PhD[1,2], and Sylvie Nguyen The Tich, MD, PhD[6,12], on behalf of the Accident Vasculaire Cérébral du nouveau-né (AVCnn; [Neonatal Stroke]) Study Group*

Objectives To evaluate the epileptic, academic, and developmental status at age 7 years in a large population of term-born children who sustained neonatal arterial ischemic stroke (NAIS), and to assess the co-occurrence of these outcomes.

Study design A cohort study including 100 term newborns with NAIS was designed. Two infants died during the neonatal period, 13 families were lost to follow-up, and 5 families declined to participate in this evaluation. Thus, 80 families completed the 7-year clinical assessment. Epileptic status, schooling, motor abilities, global intellectual functioning, spoken language, and parental opinions were recorded. Principal component analysis was applied.

Results Rates of impaired language, cerebral palsy, low academic skills, active epilepsy, and global intellectual deficiency were 49%, 32%, 28%, 11%, and 8%, respectively. All were highly correlated. Eventually, 59% of children were affected by at least 1 of the aforementioned conditions. In 30% of cases, the viewpoints of health practitioners and parents did not match.

Conclusion The prevalence of severe disabilities at 7 years after NAIS is low, but most children exhibit some impairment in developmental profile. *(J Pediatr 2016;172:156-61)*.

Trial registration ClinicalTrials.gov (NCT02511249), Programme Hospitalier de Recherche Clinique Régional (0308052), Programme Hospitalier de Recherche Clinique Interrégional (1008026), and EudraCT (2010-A00329-30).

Although perinatal ischemic stroke (PIS) is common,[1,2] its long-term outcomes remain poorly understood. Two main biases limit the accuracy of most studies: heterogeneity/small size of the sample and too short or informal follow-up.

The first consideration is that PIS encompasses several disease states that differ in pathophysiology, timing of occurrence, and clinical presentation.[1,3] Thus, it is not surprising that outcome depends primarily on the subtype of stroke. For example, nearly all children who suffer an arterial presumed PIS or a fetal periventricular venous infarction have motor impairment, compared with one-third of those with a neonatal arterial ischemic stroke (NAIS; ie, arterial PIS with clinical manifestations before the 29th postnatal day).

Age at evaluation also plays a major role. Indeed, even though the original lesion in NAIS is focal and nonprogressive, its consequences within the maturing brain as a whole are amplified over time, compounded by environmental impacts, and thus affecting all dynamic and multidimensional fields of development.[4]

The AVCnn (Accident Vasculaire Cérébral du nouveau-né [neonatal stroke]) Study gives us the opportunity to monitor a cohort of term-born children having

AVCnn	Accident Vasculaire Cérébral du nouveau-né (neonatal stroke)	PCA	Principal component analysis
BFMF	Bimanual Fine Motor Function	PIS	Perinatal ischemic stroke
CP	Cerebral palsy	PRI	Perceptual Reasoning Index
FSIQ	Full-scale IQ	PSI	Processing Speed Index
GMFCS	Gross Motor Function Classification Scale	VCI	Verbal Comprehension Index
NAIS	Neonatal arterial ischemic stroke	WISC-IV	Wechsler Intelligence Scale for Children–Fourth Edition
		WMI	Working Memory Index

From the [1]Centre Hospitalier Universitaire (CHU) Saint-Étienne, French Center for Pediatric Stroke/Pediatric Physical and Rehabilitation Medicine Department and Institut national de la santé et de la recherche médicale Centre d'investigation Clinique (INSERM CIC) 1408; [2]INSERM and University of Lyon, Dysfonction vasculaire et hémostase (DVH) Team–Unité mixte de recherche (UMR) 1090 Sainbiose, Saint-Étienne, France; [3]Assistance publique-Hôpitaux de Paris (AP-HP), French Center for Pediatric Stroke/Pediatric Neurology Department, University Hospital Necker-Enfants Malades; [4]INSERM and University of Paris 5, Thérapeutiques innovantes en hémostase–UMRS1140, Paris, France; [5]Physical and Rehabilitation Medicine Department, L'Université Nantes Angers le Mans (LUNAM) CHU Angers; [6]Laboratoire Angevin de Recherche en Ingénierie des systèmes (LARIS)-EA7315, LUNAM Université Angers, Angers, France; [7]Pediatrics Department, Centre hospitalier (CH) Côte-Basque, Bayonne, France; [8]Pediatrics and Medical Genetics Deparment, CHU Brest, Brest, France; [9]Dynamique des capacités humaines et des conduites de santé -Laboratory Epsylon EA4556, Université Montpellier 3, Montpellier, France; [10]Mines Alès, Laboratoire de génie informatique et d'ingénierie de production (LG2IP), Nimes, France; [11]Pediatric Neurology, Pediatric Subspecialties Service, Children's Hospital, Geneva University Hospital, Geneva, Switzerland; and [12]Neuropediatrics Department, LUNAM CHU Angers, Angers, France

*List of additional AVCnn Study Group members is available in the **Appendix** (available at www.jpeds.com).

Funded by Ministère de la santé et des solidarités (0308052 and 1008026), Centre hospitalier universitaire de Saint-Étienne (085), Fondation motrice, Fondation Garches, Association des paralysés de France, and Fondation de France. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.01.069

suffered an NAIS. Here we present the clinical evaluation of these children at age 7 years. As observed in multiple situations with early brain insult, our hypothesis was that developmental disabilities co-occur, along with epilepsy.[2,5-12]

Methods

The objective of the AVCnn study was to better delineate the risk factors, clinical and imaging presentation, mechanisms, and outcomes of NAIS, while avoiding the confounders described above. The study was conducted in accordance with international ethical standards and the Declaration of Helsinki. The current evaluation at age 7 years was approved by the Regional Ethics Committee in May 2010. Informed consent was obtained from each participant. The reporting of results follows the general guidelines for observational studies.[13]

The study design is a birth closed-cohort study.[14] NAIS was defined as "a focal disruption of arterial cerebral blood flow, causing neurological symptoms and confirmed by neuroimaging (computed tomography and/or magnetic resonance imaging, centrally reviewed for all cases) after birth and before the 29th postnatal day."[3] A total of 100 newborns (62 boys) were enrolled between November 2003 and October 2006 in 39 units distributed throughout France. To eliminate the consequences of prematurity, only term newborns were included. Patients with fetal stroke, cerebral sinovenous thrombosis, presumed PIS, or diffuse ischemic lesions were excluded. Clinical and imaging neonatal findings and outcomes at ages 2 and 3.5 years have been reported previously.[14-16]

Assessment at age 7 Years

Regular contacts with the families and local physicians have been maintained since enrollment. Formal encounters took place during the systematic visits at ages 1, 2, and 3.5 years. Annual newsletters were sent to keep the families informed of the results of the ongoing study and the planned evaluations.

In 2010, families were asked via mailed letters to participate in the 7-year assessment. Those who accepted were contacted by phone by the study coordinators in the months before the child's seventh birthday and invited to attend a presentation on the current project. The encounter took place over an entire day in a medical setting close to the family residence. The evaluation team included a neuropsychologist, a speech therapist, and either a pediatric neurologist or a pediatric physical and rehabilitation medicine practitioner. All expenses were supported by the AVCnn study.

Three main categories of data were recorded: (1) history since the neonatal period; (2) developmental profile; and (3) parent opinions regarding the child's present function. The following items were documented: (1) medical history, notably the occurrence of seizures; (2) schooling; (3) gross and fine motor abilities; (4) global intellectual functioning; (5) spoken language; and (6) a single closed question to the family: "Do you consider that your child suffers any sequelae of his/her neonatal event?"

Variables and Endpoints

Epilepsy was defined as the occurrence of 2 or more afebrile unprovoked seizures after the neonatal period or, in the case of a single afebrile unprovoked seizure, the initiation of antiepileptic treatment. Epilepsy and seizures were classified according to the current International League Against Epilepsy terminology and classification scheme.[17] Seizure-free at age 7 years was defined as the absence of seizures and treatment for >1 year. Otherwise, epilepsy was classified as active.

Depending on the date of assessment, the child's expected level was either first or second grade. Grade retention, the need for specific and individualized support in a mainstream school, and inclusion in a special school were considered to represent low academic skills.

Three main domains were assessed for the developmental profile. Motor evaluation was focused on the presence of cerebral palsy (CP). The definition given by the Surveillance for CP in Europe was used: permanent abnormal tone or decreased strength as a consequence of a nonprogressive early brain insult, and associated with a patent functional deficit.[18] Motor impairment was further classified with the Gross Motor Function Classification Scale (GMFCS), according to the child's level of gross motor abilities. In the GMFCS schematic, level I subjects walk without limitations, and level V subjects need a manual wheelchair.[19] The Bimanual Fine Motor Function (BFMF) tool was used to assess the ability to grasp, manipulate, and hold objects for each hand separately (level 0, no impairment; level 5, only ability to hold or worse with both hands).[20]

Global intellectual ability was evaluated using the 4 indices of the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV): Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Global intellectual deficiency was defined as a full-scale IQ (FSIQ) <70. As recommended in WISC-IV Administration and Scoring Manual, when excessive discrepancies between indices precluded the composite FSIQ score validity, only subscores were provided. Global intellectual deficiency was then considered when both VCI and PRI were <70.

Finally, the standardized spoken language assessment Nouvelles Epreuves pour l'Examen du Langage was performed.[21] This battery was validated to test the language profile of 3.5- to 8.5-year-old French-speaking children, including speech and sound abilities as well as expressive and receptive lexicosemantic and morphosyntactic skills. Children with a score >2 SD below the mean for 1 of the 4 linguistic components (ie, not including isolated speech and sound delay) were considered to have impaired language.

Biases

Some families could not be contacted or declined to participate in the present evaluation, and thus the final rate of disabilities could have been misestimated. This incomplete follow-up did not alter the relationship between variables, however, because hypotheses were applied only to those