Outcome of stroke in Saudi children

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ABSTRACT

Objective: To report on the prognosis, neurologic outcome, and recurrences of stroke in Saudi children.

Methods: We evaluated a cohort of 104 Saudi children with stroke at the Division of Pediatric Neurology at King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia from July 1992 to February 2001 (retrospective study) and February 2001 to March 2003 (prospective study). We analyzed the salient clinical, neuroimaging, neurophysiological, neuropsychological and laboratory data following retrieval from a specialty designed comprehensive protocol.

Results: Of the 104 children in the cohort (aged one month to 12 years), 5 (4.8%) died during the study period and 9 (8.7%) were lost to follow-up. The mean duration of follow-up for the remaining 90 children was 40 months (median 33 months). Recovery was judged complete in 6 (6.7%) of these 90 children. We detected residual hemiparesis (irrespective of its effect on daily functions) in 73 (81%) and this was combined with other motor deficits in 45 children (50%). Forty-one children (46%) had residual dysphasia or language deficits, whereas 45 (50%) were judged to have had cognitive deficit. Psychometry revealed an abnormal intelligence quotient test (<70) in 19 of 26 (73%) children. Other neurologic sequelae included epilepsy in 52 (58%), recurrent headaches in 13 (14%) and hydrocephalus in 4 (4.4%) patients. Six of the 95 (6.3%) children, who were ascertained to have died or kept their follow-up, had one or more recurrences, one month to 5 years after the initial stroke (median 23 months). Patients who had recurrent strokes were significantly more likely to be the product of consanguineous marriages (p=0.04). Regarding the group of 23 children with perinatal stroke, neither deaths nor recurrences occurred during the follow-up period. However, 20 (87%) of them had significant delays in their developmental milestones.

Conclusions: The toll of stroke in Saudi children is demanding, with most children demonstrating persistent neurologic or cognitive deficits. Primary prevention for recurrences is feasible through informed genetic counseling.

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Studying the outcome of childhood stroke is necessary to understand the likely impact of stroke prevention and treatment strategies, given the fact that surviving children, and their families, have to cope with many disabled years ahead of them.[1] The outcome of childhood stroke depends on the age of the patient, etiological risk factor, and the type of stroke, associated symptoms at onset, and the location of the lesion.[2-9] Children less than 2 years of age who develop cerebral infarction are more likely to have intellectual and behavioral difficulties.[10] Those with parainfectious, idiopathic or treatable causes generally have no recurrence.[11] The latter include operable lesions and resectable or successfully embolized arteriovenous malformation.[12] However, some forms of cardiac surgery (for example, Fontan procedure) may improve the child's cardiac function, yet have the potential risk of subsequent stroke.[13,14] Certain metabolic causes (such a homocystinuria) are amenable to treatment and dietary management.[11] In children, hemorrhagic stroke is more likely to end fatally than ischemic stroke.[15] Seizures at the onset of ischemic stroke are more likely to be followed by intellectual impairment and behavior problems.[16]

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Also, less language deficit was noted following left hemisphere infarction in children who were more strongly left handed.[17] In the present study, we explore the prognosis, neurologic outcome and recurrences of stroke in a cohort of 104 Saudi children followed during a retrospective and prospective study on childhood stroke.

Methods. The cohort included 104 Saudi children, who presented with stroke and were evaluated and followed-up at the Division of Pediatric Neurology, at King Khalid University Hospital (KKUH), College of Medicine, King Saud University, or were in-patients in the pediatric wards at KKUH, Riyadh, Kingdom of Saudi Arabia. The duration of the prospective study was 2 years (February 2001–March 2003), whereas the retrospective study extended for 8 years and 7 months (July 1992-February 2001). The salient demographic, clinical, neuroimaging, neurophysiological and laboratory data were retrieved in a specially designed comprehensive protocol. Details of these, as well as the laboratory methods and statistical analyses are depicted elsewhere.[18,19] Neurodevelopmental and psychosocial tests, used during the study, included Denver Developmental Screening Test, Vineland Adaptive Behavior Scales, Stanford-Binet Intelligence Scale and Wechsler Intelligence Scale for children. On psychometric tests, an intelligence quotient (IQ) of <70 was considered to indicate mental retardation.

Results. The cohort of 104 Saudi children (aged one month to 12 years) consisted of 56 males and 48 females. The mean age at onset of stroke was 27.1 (SD±39.3) months (median 6 months), and was similar in boys and girls.[18] Their outcome is outlined in **Figure 1**. Five children died during the study period, giving an overall case fatality rate of 4.8%. Nine (8.7%) patients were lost to follow-up. The mean duration of follow-up for the remaining 90 patients was 40 months (median = 33 months). Recovery was judged complete in 6 (6.7%) of these 90 children. Residual hemiparesis combined with other motor deficits was detected in 45 children (50%). Psychometry revealed an abnormal IQ test (<70) in 19 of the 26 (73%) children who availed for the test. Six of the 95 (6.3%) children, who were ascertained to have died

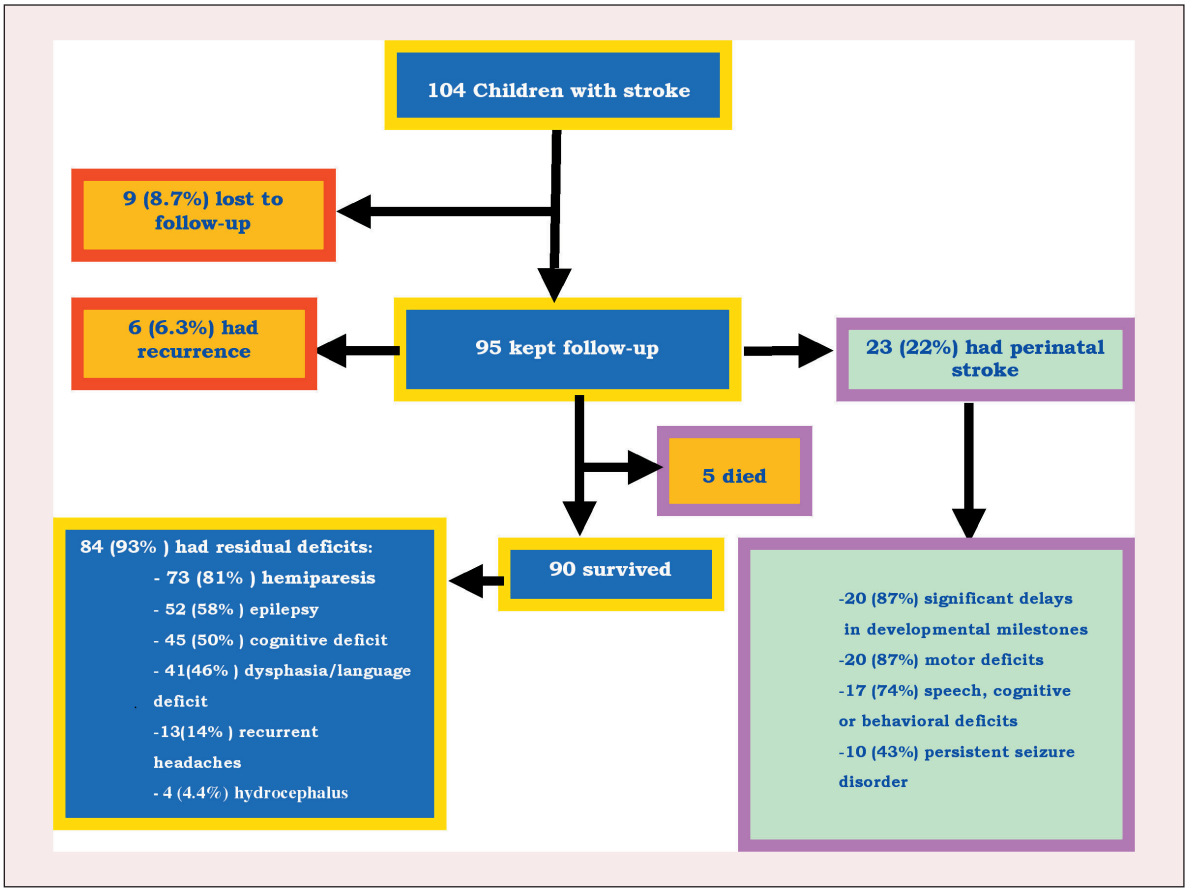

Figure 1 - Outcome of stroke in 104 Saudi children followed for a mean duration of 40 months (median = 33 months).

or kept their follow-up, had one or more recurrences, one month to 5 years after the initial stroke (median 23 months). Patients who had recurrent strokes were significantly more likely to be the product of consanguineous marriages (p=0.04). Four of these children had moyamoya syndrome associated with sickle cell disease (SCD) in one patient; membranous ventricular septal defect combined with sickle cell – β – thalassemia (SCβ^0-thalassemia) in another; cutis laxa (wrinkly skin syndrome) in the third and protein C deficiency in the fourth. The remaining 2 patients included one who had Sturge-Weber syndrome combined with Klippel-Trenaunay syndrome; and a girl who had mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and died at the age of 33 months, 17 months after the onset of the initial stroke.

Regarding the group of 23 children with presumed perinatal ischemic injury, neither deaths nor recurrences occurred during the follow-up period **(Figure 1).** Most of these patients had significant delays in their developmental milestones. Global delays involving gross motor, fine motor/adaptive, and language and social/personal parameters were recorded in 13 (57%) children. At the time of examination, motor deficits were detected in 20 patients. This consisted of hemiparesis in 13, bilateral motor deficit in 5, and monoplegia (with or without dystonic posture of one hand) in 2 children. Residual facial paralysis was found in 2 patients. Visual impairment was detected in 4 children, and hearing impairment was detected in 2 children. Seven patients had complex partial seizure with secondary generalized tonic-clonic seizures in 3 of them. Two children had infantile spasms, and a third had Lennox-Gastaut syndrome.

Discussion. The case fatality rate in the present series was 4.8%, recovery was judged complete in only 6.7%, and residual hemiparesis (irrespective of its effect on daily function) was detected in 81%, and was combined with other motor deficits in 50%. Data from the Canadian Pediatric Ischemic Stroke Registry, which included 420 children with arterial ischemic stroke (AIS) and 160 children with sinovenous thrombosis (SVT) revealed that 12% of children were dead by the outcome evaluation, 27% were neurologically normal, and 61% were abnormal.[20] In a study on stroke among Hong Kong Chinese children,[21] 50 patients were identified in an 11-year period. The mortality was 18%, and long-term neurologic deficits occurred among 41% of survivors. Another study[22] on childhood ischemic stroke in a non-urban USA population reported no deaths in 27 children who were identified in a 10-year period. However, 77% had mild, moderate, or severe neurologic impairments. A 3-year population-based, prospective Swiss Neuropediatric Stroke Registry,[9] which included 80 children, reported an overall mortality of 6%, and moderate/severe neurologic sequelae in 45% of those who had childhood AIS. Prognosis of hemorrhagic stroke seems to be worse. In a study of Blom et al,[23] 20 of 56 children (36%) who had hemorrhagic stroke (at a mean age of 7.7 years) were dead at a mean follow-up period of 10.3 years. Of the 31 patients who could be examined, no physical impairment was observed in 15 (48%). In another study by Al-Jarallah et al,[24] the case fatality rate was 8.8% and 50% of the patients regained normal neurologic function. As a whole, prospective, longitudinal studies showed recovery without obvious neurological deficits in approximately one third of neonates and children after AIS.[25,26] The relatively low case fatality rate in our study is conceivably explained by the fact that many stroke patients might have died before having access to an appropriate medical facility or effective intervention in their districts. Those who manage to reach the tertiary care service at KKUH were the more medically stable. A vivid illustration of this is to be found in the 2 brothers with hemophilia B.[19] The older one was referred from a regional hospital and was declared brain dead shortly after arrival to KKUH. His younger brother presented primarily to KKUH with intracerebral bleed, which was successfully managed both medically and surgically. Complete recovery (as judged by clinical evaluation) was less in this study compared to others since motor deficit was counted irrespective of its effect on daily function.[27] However, other factors might have been operating. Seizures at presentation of stroke and certain neuroimaging abnormalities are associated with a poor outcome. Infarct volume >10% of intracerebral volume has a poorer outcome.[20]

Less obvious residual deficits were also common in our cohort of 104 Saudi children since 46% had dysphasia or language deficit, and 50% were judged to have cognitive deficit. In the study by deVeber et al[26] on neurologic outcome in survivors, which included 133 children with AIS, and 38 with SVT, followed for a mean of 2.1 years (range, 0.8-6.6 years), the primary outcome was normal in 37%, mild deficit in 20%, moderate deficit in 26%, and severe deficit in 16%. Deficits and outcome were based on a scoring system, which included sensorimotor, language, cognitive, and behavioral functions. Regarding hemorrhagic stroke, the degree of recovery was found to vary with the size and intracranial location of the hemorrhage. Of 68 children with non-traumatic brain hemorrhage, aphasia was found in 7.4% and various cognitive

defects were documented in 9 (13.2%) children.[24] In a more recent study with a larger mean follow-up period of 10 years, signs of cognitive deficits were found in 15 of 31 (48%) patients with hemorrhagic stroke.[23] The contribution of SCD to the occurrence of developmental disabilities is well-documented and significantly impaired cognitive functioning was observed in SCD patients with a history of stroke.[28,29] Factors known to predict poorer outcome in children with AIS include the presence of large volume of infarct, stroke after the neonatal period, seizures at onset of stroke, progressive vasculopathy, congenital heart disease and the occurrence of multiple risk factors.[25-27,30] It is also noteworthy that remarkably more children in our study (58%) had persistent seizure disorder compared to the figures (7-17%) reported internationally.[21,22,30]

The impact of stroke in the subgroup of children in our study with perinatal stroke deserves special note since intellectual outcome is partly influenced by the patient's age at injury.[31] Most had significant delays in their developmental milestones and motor deficits were detected in 87%. This is similar to the findings of Golomb et al[32] who observed clinically significant persistent hemiparesis (interfering with hand function, gait, or both) in 21 of 22 patients. They also noted that although hand preference caused by infarction does not completely resolve, yet the eventual handicap might be mild. A study by Mercuri et al[33] to assess neuromotor function at school age in 22 children who had cerebral infarction on neonatal MRI, revealed that 60% had residual hemiplegia or some neuromotor abnormality such as asymmetry on the neurologic examination or poor scores on the neuromotor test with no signs of asymmetry. In an earlier review of 579 infants with perinatal arterial stroke (PAS), 40% were neurologically normal at follow-up.[34] However, in a more recent population-based study, Wu et al[35] observed that a delayed presentation of motor deficits was associated with a more severe degree of motor impairment among infants with PAS. Comparatively, the majority of children with perinatal stroke in our study showed signs of speech, cognitive and behavioral deficits and 43% developed persistent seizure disorder. The corresponding figures in the study of Golomb et al[32] were 50% for speech, learning or behavioral problems, and 23% for persistent seizure disorder. However, in both studies, eventual impairment might have been overestimated since children with resolution of early hand preference may escape detection. Also, a longer duration of follow-up period is needed for the estimation of final impairment. This has been one of the limitations of the present study with a mean duration of follow-up of <4 years.

The stroke recurrence rate in this series was 6.3% with median follow-up period of 33 months (range one month-5 years). The reported overall risk of recurrent AIS in children ranged between 6-32%,[21,26,27,36-40] and this wide range reflects differences in etiology of stroke in the various studies, and whether the definition was clinical or radiological. Although stroke recurrences and transient ischemic attacks have been reported several years after the primary event, in most cases these happen within the first 6 months.[41,42] It is noteworthy that the follow-up period for our prospective study group of 23 children (seen during the last 2 years of the study) was short.

Four of the 6 children who had recurrences in this study had moyamoya syndrome, which has been associated with other diseases in all of them (SCD and SCβ^0-thalasemia in 2 patients, cutis laxa [wrinkly skin syndrome] in the third and protein C deficiency in the fourth). The other two included a boy who had Sturge-Weber syndrome associated with Klippel-Trenaunay syndrome and a girl who had MELAS. This conforms with the findings in previous reports where recurrence has been linked to moyamoya disease,[43] sickle cell anemia,[44] metabolic disease,[45] and the presence of multiple stroke risk factors.[46] It might be intriguing to note that the 4 children with moyamoya syndrome had associated diseases with clear Mendelian inheritance. Both SCD and wrinkly skin syndrome are inherited as autosomal recessive,[47] whereas protein C deficiency is inherited as an autosomal dominant disorder.[48] Primary prevention is feasible in all of them through informed genetic counseling.

In conclusion, the toll of stroke in Saudi children is tasking, with the majority of children demonstrating persistent neurologic and cognitive deficits. Informed genetic counseling remains the cornerstone for primary prevention of recurrences.

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