ORIGINAL RESEARCH PAPER

Volume-8 | Issue-8 | August - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MONOGENIC CONDITIONS ASSOCIATED WITH ISCHEMIC STROKE

Neurology

Pushpendra N Renjen Sr. Consultant Neurologist & Academic Coordinator, Institute of Neurosciences, Indraprastha Apollo Hospitals

Dr. Dinesh Chaudhari* Associate Consultant, Institute of Neurosciences.Indraprastha Apollo Hospitals – 110076*Corresponding Author

Dr Anjali Mishra FNB Critical Care, Max Super speciality Hospital, New Delhi

Dr Abhas Kumar DNB Neurology, Institute of Neurosciences. Indraprastha Apollo Hospitals – 110076

ABSTRACT

Monogenic conditions account for a considerable proportion of patients with cryptogenic stroke. In some disorders stroke is the prevailing manifestation whereas in others it is part of a wider phenotypic spectrum. The identification of stroke cases caused by monogenic disorders is important both for therapeutic decisions and genetic counselling, although they represent less than 1% of all stroke patients. This article emphasizes on genetic, pathological, and clinical features of single-gene disorders related to ischemic stroke.

KEYWORDS

Monogenic, Stroke, CADASIL, Fabry, Marfan

INTRODUCTION -

Monogenic conditions account for a considerable proportion of patients with cryptogenic stroke [1]. In some disorders stroke is the prevailing manifestation whereas in others it is part of a wider phenotypic spectrum (Table l). Most single gene disorders are associated with specific stroke subtypes, which together with the accompanying systemic manifestations may lead to diagnosis.

CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a small vessel disease due to mutations in NOTCH3 [2]. The clinical "phenotype encounters recurrent TIAs and strokes, progressive cognitive impairment and psychiatric disturbance with onset in early to mid-adulthood. About one third of patients develop migraine with aura [3-4]. Neuroimaging findings are similar to sporadic small vessel disease (SVD). A diagnostically important feature of CADASIL, however, is bilateral involvement of the anterior temporal white matter and external capsule [5-6].

NOTCH3 encodes a cell surface receptor, which has a role in arterial development and is expressed on vascular smooth muscle cells (VSMC). Mutations are greatly stereotyped in that most if not all mutations change the number of cysteine residues within one of the extracellular epidermal-growth-factor-like repeat domains [7-8].

Table 1: Single gene disorders associated with Ischemic Stroke

There have been single reports on mutations not involving cysteine residues [9] but the role of these sequence variants remains controversial. The mutational spectrum is broad. About 95% of the patients have missense mutations which cluster in the first few exons. Preliminary evidence suggests there are specific mutations are associated with a slightly more aggressive phenotype [10-11].

The mechanisms by which NOTCH3 mutations become pathogenic are still poorly understood. Most mutations do not seem to interfere with Notch3 receptor signaling [11]. However, studies in patients and transgenic animals have shown that the mutant Notch3 receptor accumulates in arteries and precapillaries [12-13]. Electron microscopy shows granular osmiophilic deposits within the vascular basal lamina, which are specific for CADASIL, present throughout the arterial system and can therefore be used for diagnostic purposes [14].

Fabry disease -

Condition	Gene	Stroke Mechanism	Associated clinical features	Diagnostic test
CADASIL	NOTCH3	Small vessel disease	Migraine with aura	Mutational screening, Skin biopsy
Fabry Disease	Gal	Large artery disease and small vessel disease	Angiokeratoma ,neuropathic pain ,acroparaesthesia ,hypohydrosis,corneal opacities,cataract ,renal failure,cardiac failure	α-galactosidase activity, Mutational screening
Sickle cell disease	HBB	Large artery disease, Small vessel disease, Hemodynamic insufficiency	Pain Crisis, bacterial infection , vaso-occlusive crises, pulmonary and abdominal crises, anemia, myelopathy , seizure	Peripheral blood smear, Electrophoresis, Mutational analysis
Homocystinuria	CBS and others	Large artery disease,cardioembolism, Smallvessel disease,arterial Dissection	Mental Retardation, atraumatic dislocation of lense, skeletal abnormalities(Marfan-like),premature atherosclerosis, thrombo-embolic events	Urine analysis, Plasma Levels of homocysteine and methionine, (Mutational screening)
MELAS	Mitochondrial DNA	Complex(microvascular and neurnol factor)	Developmental delay, sensorineural hearing loss, short stature, seizures, episodic vomiting diabetes, migraine-like headache, cognitive decline	Muscle biopsy, Mutational analysis of mtDNA

Marfan Syndrome	FBN1	Cardioembolism and Arterial dissection	Pectus carination or excavatum, reduced upper-t lower- segment ratio or arm span height ratio, scoliosis>20%, ectopia lentis, dilation or dissection of the ascending aorta, lumbosacral dural ectasia	Clinical diagnosis , (Mutational screening)
Ehlers- Donlos Syndrome Type IV	COL3A1	Arterial dissection	Easy bruising, thin skin with visible veins, typical facial features, rupture of arteries , uterus, ort intestines	Biochemical studies Mutational screening
Pseudoxanthoma elasticum	ABCC6	Large artery disease and Small vessel disease	Skin changes (increased elasticity and yellow-orange popular lesions), Ocular changes (angioid streaks), Hypertension	Skin biopsy, Mutational screening

Fabry disease (FD) is an X-linked systemic disorder due to deficiency of the lysosomal enzyme α-" galactosidase A. α-gal A deficiency results in progressive accumulation of glycosphingolipids, (in particular globotriaosylceramide, GB3) in the myocardium, renal epithelium, skin, eye and vasculature. Symptoms often begin in childhood or adolescence with acroparesthesia, angiokeratoma, or hypohidrosis being frequent signs. Systemic complications involving the kidneys, heart and brain usually follow in mid adulthood.

FD is surprisingly common among young stroke patients. In a recent large series of young (18-55 years) patients with cryptogenic stroke 4.9% of the males and 2.4% of the females were found to carry a functionally relevant α-GAL mutation [1]. Cerebrovascular symptoms occur from both large artery disease (LAD) and SVD with a preference for the posterior circulation [15-16-17-1]. The SVD in FD is reflected by white matter changes and recent work suggests that the extent of such lesions is influenced by polymorphisms in the genes for interleukin-6, endothelial nitric oxide synthase (eNOS), factor V, and protein Z [18]. These findings on potential modifier genes are promising but await confirmation.

FD may be suspected based on the associated systemic signs (Table l) and confirmed by measuring α-gal A activity or by screening for mutations. In women, measurements of enzyme activity are less reliable because of skewed inactivation of the X-chromosome in female mutation carriers. The mutational spectrum is broad. Most patients carry missense or nonsense mutations in the coding region of the GAL gene. Enzyme replacement therapy with recombinant α-gal A is effective in reducing GB3 deposition and ameliorating some of the symptoms [19-20]. However, a benefit on stroke has not been demonstrated.

MELAS

The syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is associated with several mutations in mitochondrial DNA [21-22]. About 80% of patients carry an A to G transition at position 3243 in the $tRNA^{leucine(UUR)}$ gene. The second most common mutation (T3271C) is found in about 10% of cases. The relative distribution of mutant and wild type mtDNA may vary in different tissues explaining in part the immense phenotypic diversity of mitochondrial disorders. MELAS is associated with a variety of symptoms (Table 1). However, monosymptomatic cases with stroke as the sole manifestation do exist.

The cerebral lesions underlying strokes-like episodes in MELAS differ from typical ischemic infarcts. The cortex is almost invariantly involved. In many cases, lesions are not limited to vascular territories and there are no embolic or stenotic lesions on angiography. Finally, MRI may show changes consistent with vasogenic rather than cytotoxic edema [23]. These observations point toward mechanisms other than pure ischemic infarction. Current hypotheses include i) a disturbance of the blood-brain barrier, ii) impaired autoregulation of cerebral blood flow [24], and iii) primary defects in neuronal oxidative metabolism. Lesions may spread over time or markedly regress on subsequent scans [25].

Connective tissue disorders

IS is a well-known complication of several heritable connective tissue disorders.

Marfan syndrome (MFS) is an autosomal dominant systemic condition affecting the musculoskeletal system, cardiovascular system and eye [26]. The diagnosis is usually established on clinical grounds (27] and Table 1) whereas the role of genetic testing remains limited. MFS is caused by mutations in a very large gene(FBN-1; 65 exons) and more than 90% of families have a private mutation which renders mutational screening very laborious [28]. FBN1 encodes fibrillin 1 an extracellular matrix protein. Fibrillin 1 is expressed in many tissues including the heart and elastic arteries. It shares homology with the transforming growth factor β (TGFβ) binding proteins and there is increasing evidence for a key role of TGFβ signalling in MFS [28-26]. Cerebrovascular complications of MFS include transient ischemic attacks (TIA), ischemic infarcts, and subdural hematoma. In a retrospective series on 513 patients neurovascular manifestations were associated with cardiac sources of embolism, in particular prosthetic heart valves, mitral valve prolapse and atrial fibrillation whereas there was no association with aortic disease or cerebral artery dissection [30]. However, other studies have observed an association with aortic and cerebral artery dissection [31-32]. Further causes of IS include chronic anticoagulant therapy and perioperative embolic events in patients undergoing aortic root replacement [33].

Ehlers-Danlos syndrome (EDS) type IV, the vascular type, is an autosomal dominant condition resulting from mutations in COL3A1, the gene for collagen type III [34]. EDS may be suspected based on the associated clinical features (table 1) and confirmed by mutational screening or biochemical studies on cultured fibroblasts (synthesis of an abnormal type III procollagen).

The mutational spectrum is broad and neomutations are frequent [34]. About 50% of the index cases have no apparent family history. Cerebrovascular complications are common and include intracranial aneurysms, arterial dissection and spontaneous rupture of large and medium sized arteries [35-36]. In a series of 419 patients 10.5% had neurovascular complications [34]. Carotid artery dissection and fistulae involving the carotid artery were the most frequent findings.

IS has also been recognized as a complication of osteogenesis imperfecta and pseudoxanthoma elasticum [36] which is associated with stenotic lesions of the distal carotid artery and SVD [36-37] (Table 1).

Sickle cell disease

Sickle cell disease (SCD) is the most common cause of stroke in children [38]. SCD may be caused by the homozygous state for Hemoglobin S (HbS) or by the compound heterozygous state with other hemoglobinopathies such as HbC or β-thalassaemia [39]. HbS results from an amino acid substitution in the β-chain.

About 25% of patients with HbS/HbS and 10% of those with HbS/HbC will have a stroke by the age of 45 years [40]. The incidence of IS is highest between 2 and 5 years and lowest between 20 and 30 years. Conversely, the risk of hemorrhagic stroke is highest in the third decade [40]. Stroke recurrence is frequent. Clinically overt strokes are typically due to LAD. The latter is characterized by intimal thickening, proliferation of fibroblasts and smooth muscle cells and eventually thrombus formation. It is usually confined to the supraclinoid internal carotid artery and the proximal portions of the middle and anterior cerebral artery [41]. Ischemic infarcts are frequently located in borderzone regions in particular the anterior and deep borderzone region [42-38]. Apart from overt stroke many patients develop silent

infarcts [43-38]. These infarcts are small, located in subcortical regions, and attributed to SVD.

A critical component in the pathogenesis of both LAD and SVD is an abnormal interaction between sickled red blood cells and the vascular endothelium [44-38]. Sickled red blood cells tend to adhere to the endothelium thus favouring thrombus formation and vascular occlusion. Endothelial activation further promotes remodelling of the arterial wall and vasculopathy.

The risk of stroke in SCD seems to be strongly influenced by modifier genes [45-46-47]. In fact, the stroke phenotype in SCD has become a prominent example of modifying genetic influences in mendelian traits. An inhibitory effect of fetal haemoglobin (HbF) on the polymerization of HbS has been known for many years. Concentrations of HbF are under genetic control and have a major impact on SCD in general. A more specific effect on stroke has been demonstrated for polymorphisms in various genes involved in inflammation and cell adhesion. Thus for example, polymorphisms in the cell adhesion molecules VCAM and P-selectin were found to be associated with stroke risk in SCD [48-49-50]. Also, there is evidence for a role of the interleukin-4-receptor gene in determining stroke risk [49]. A major methodological step has been the use of Bayesian networks. By applying such networks to a large number of single nucleotide polymorphisms (SNPs), Sebastiani and colleagues [50] identified 31 SNPs in 12 genes that were found to interact with HbF in modulating stroke risk. The network included P-selectin and several genes in the TGF β pathway, which has been associated with stroke in other studies. Remarkably, this network accurately predicted the occurrence of stroke in an independent sample based on genotyping of just a few SNPs. These observations highlight the importance of modifier genes in monogenic conditions. They further emphasize a potential role of genetics in predicting stroke risk. The risk of stroke in SCD can be markedly reduced by transfusion therapy [51-38]. Yet, chronic transfusion may cause problems and identifying patients at risk of stroke remains a challenge. In this regard, screening methods based on genotyping are a potentially important approach [46].

Homocystinuria

Homocystinuria encompasses a group of mostly autosomal recessive enzyme deficiencies which cause high (>l00µmol/L) plasma levels of homocysteine (Hcy) and homocystinuria. The disease should be considered in any child with stroke, mental retardation, atraumatic (mostly downward) dislocation of the ocular lenses or Marfan-like skeletal abnormalities. Homocystinuria must be distinguished from milder (15 to l00µmol/L) hyperhomocysteinemia which is a risk factor for stroke in the general population and associated with deficient dietary B6, BIZ or folate and with a polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene. The most common cause of homocystinun'a is a deficiency of cystathionine beta-synthase (CBS) a key enzyme in the degradation of Hcy [52]. More rarely, homocystinuria results from disturbances in the convenion of homocysteine to methionine by a pathway that requires the formation of methylated derivatives of folate and B12.

About 50 percent of untreated patients with CBS deficiency have a thromboembolic event by the age of 30 and about one third of these events involve the cerebrovascular system [52]. Homocystinuria may cause stroke not only through atherosclerosis and thromboembolism but also through SVD and arterial dissection [53-54]. Homocysteine has been shown to injure endothelial cells and increase smooth muscle cell proliferation in vitro [54]. Putative factors whereby homocysteine may induce vascular injury further include extracellular matrix modification, lipoprotein oxidation and effects on platelets and coagulation [55]. Patients with concurrent homocystinuria and factor V Leiden have an increased risk of thrombosis [56].

Approximately half of the patients with CBS deficiency respond to B6. Those who respond tend to have a later onset, a milder phenotype and a better prognosis [57]. The mutational spectrum of CBS deficiency is broad [58]. There are many private mutations but some mutations, in particular I278T and G307S, are relatively common [58-59]. An important observation regarding genotype-phenotype correlations has been that some mutations including A114V and I278T are associated with B6 responsiveness whereas others, in particular G307S are associated with B6 resistance. Early diagnosis of homocystinuria is essential, as complications can be minimised by early treatment.

MISCELLANEOUS

Ischemic stroke may occur as a complication of several heritable cardiomyopathies, dysrhythmias, hemoglobinopathies, coagulopathies, dyslipidemias, and vasculopathies. In some cases, an association with stroke has been firmly established. In many others an association is less well documented or a matter of controversy.

CONCLUSION –

In the majority of cases, a specific single-gene disorder is related to a specific stroke phenotype, although some disorders, such as FD, predispose to stroke by more than one mechanism. Vascular and parenchymal lesions seen with MRI and angiography could be a good support to the clinical diagnosis. In patients with CADASIL or FD,

the brain MRI can show specific lesion patterns, and in Moyamoya disease, angiography findings could be diagnostic. Another rapid and noninvasive investigation is skin biopsy, which permits the diagnosis to be addressed in a number of cases (CADASIL, hereditary endotheliopathy with retinopathy, nephropathy, and stroke, Fabry, PXE, and EDS). Therefore, the presence of specific clinical systemic features, in addition to young age at stroke onset, the lack of vascular risk factors, and a positive family stroke history could suggest a single-gene disorder. Thus specific diagnostic tools can aid the diagnosis, but genetic screening is nearly always necessary to confirm the diagnostic suspicion.

REFERENCES -

1. Rolfs A, Bottcher T, Zschiesche M at al. Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study Lancet. 2005 Nov 19;366(9499):1794-6.
2. Joutel A, Corpchot C, Ducros A et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature 1996; 383: 707-710.
3. Dichgans M, Filippi M, Bruning R et al. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. Neurology 1999; 52: 1361-1367.
4. Opherk C, Peters N, Herzog J, Luedtke R, Dichgans M. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 CADASIL patients. Brain 2004; 127: 2533-2539.
5. Auer DP, Putz B, Gossl C, Elbel GK, Gasser T, Dichgans M. Differential Lesion Patterns in CADASIL and Sporadic Subcortical Arteriosclerotic Encephalopathy: MR Imaging Study with Statistical Parametric Group Comparison Radiology 2001; 218: 443-451.
6. O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology 2001; 56: 628-634.
7. Joutel A, , Vahedi K, Corpechot C, Troesch Aet al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. Lancet 1997; 350: 1511-1515.
8. Peters N, Opherk C, Bergmann T, Castro M, Herzog J, Dichgans M. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies Arch Neurol. 2005 Jul;62(7):1091-4.
9. Mazzei R, Conforti FL, Lanza PL, et al. A novel Notch3 gene mutation not involving a cysteine residue in an Italian family with CADASIL. Neurology 2004;63:561–4.
10. Lesnik Oberstein SA, van den BR, van Buchem MA, et al Cerebral microbleeds in CADASIL Neurology. 2001 Sep 25;57(6):1066-70.
11. Peters N, Opherk C, Zacherle S, Capell A, Gempel P, Dichgans M. CADASIL-associated Notch3 mutations have differential effects both on ligand binding and ligand-induced Notch3 receptor signaling through RBP-Jk Exp Cell Res. 2004 Oct 1;299(2):454-64.
12. Joutel A, Andreux F, Gaulis S, Domenga V, Cecillon M, Battail N, Piga N, Chapon F, Godfrain C, Tournier-Lasserve E. The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients J Clin Invest. 2000 Mar;105(5):597-605.
13. Ruchoux MM, Domenga V, Brulin P, Maciazek J, Limol S, Tournier-Lasserve E, Joutel A. Transgenic mice expressing mutant Notch3 develop vascular alterations characteristic of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy Am J Pathol. 2003 Jan;162(1):329-42.
14. Ruchoux MM, Chabriat H, Bousser MG, Baudrimont M, Tournier-Lasserve E. Presence of ultrastructural arterial lesions in muscle and skin vessels of patients with CADASIL. Stroke. 1994;25(11):2291–2292
15. Crutchfield KE, Patronas NJ, Dambrosia JM, Frei KP, Banerjee TK, Barton NW, Schiffmann R Quantitative analysis of cerebral vasculopathy in patients with Fabry disease. Neurology. 1998 Jun;50(6):1746-9.
16. Grewal RP. Stroke in Fabry's disease. J Neurol 1994; 241: 153-156.
17. Mitsias P, Levine SR. Cerebrovascular complications of Fabry's disease Ann Neurol. 1996 Jul;40(1):8-17.
18. Altarescu G, Moore DF, Schiffmann R. Effect of genetic modifiers on cerebral lesions in Fabry disease. Neurology. 2005 Jun 28;64(12):2148-50.
19. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 2001 Jun 6;285(21):2743-9.
20. Eng CM, Guffon N, Wilcox WR et al Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. N Engl J Med. 2001 Jul 5;345(1):9-16.
21. Pavlakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome Ann Neurol. 1984 Oct;16(4):481-8.
22. Martinez-Fernandez E, Gil-Peralta A, Garcia-Lozano R et al. Mitochondrial disease and stroke. Stroke 2001; 32: 2507-10.
23. Yoneda M, Maeda M, Kimura H, Fujii A, Katayama K, Kuriyama M. Vasogenic edema on MELAS: a serial study with diffusion-weighted MR imaging Neurology. 1999 Dec 10;53(9):2182-4.
24. Clark JM, Marks MP, Adalsteinsson E, Spielman DM, Shuster D, Horoupian D, Albers GW. MELAS: Clinical and pathologic correlations with MRI, xenon/CT, and MR spectroscopy. Neurology. 1996 Jan;46(1):223-7.
25. Iizuka T, Sakai F, Kan S, Suzuki N. Slowly progressive spread of the stroke-like lesions in MELAS. Neurology 2003; 61: 1238-1244
26. Judge DP, Dietz HC. Marfan's syndrome. Lancet 2005; 366: 1965-1976.
27. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic

criteria for the Marfan syndrome. Am J Med Genet. 1996 Apr 24;62(4):417-26.
28. Nollen GJ, Mulder BJ. What is new in the Marfan syndrome? Int J Cardiol 2004; 97 Suppl 1: 103-108.
29. Neptune ER1, Frischmeyer PA, Arking DE, et al Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. Nat Genet. 2003 Mar;33(3):407-11.
30. Wityk RJ, Zanferrari C, Oppenheimer S. Neurovascular complications of marfan syndrome: a retrospective, hospital-based study. Stroke. 2002 Mar;33(3):680-4.
31. Spittell PC, Spittell JA Jr, Joyce JW, Tajik AJ, Edwards WD, Schaff HV, Stanson AW. Clinical features and differential diagnosis of aortic dissection: experience with 236 cases (1980 through 1990) Mayo Clin Proc. 1993 Jul;68(7):642-51.
32. Schievink WI, Bjornsson J, Piepgras DG. Coexistence of fibromuscular dysplasia and cystic medial necrosis in a patient with Marfan's syndrome and bilateral carotid artery dissections. Stroke. 1994;25:2492–2496.
33. Gott VL, Greene PS, Alejo DE et al. Replacement of the aortic root in patients with Marfan's syndrome. N Engl J Med 1999; 340: 1307-1313.
34. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type N Engl J Med. 2000 Mar 9;342(10):673-80.
35. North KN, Whiteman DA, Pepin MG, Byers PH. Cerebrovascular complications in Ehlers-Danlos syndrome type IV. Ann Neurol. 1995 Dec;38(6):960-4.
36. Schievink WI, Michels VV, Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders. A review. Stroke. 1994 Apr;25(4):889-903.
37. Van den Berg JS, Hennekam RC, Cruysberg JR, Steijlen PM, Swart J, Tijmes N, Limburg M. Prevalence of symptomatic intracranial aneurysm and ischaemic stroke in pseudoxanthoma elasticum. Cerebrovasc Dis. 2000 Jul-Aug;10(4):315-9.
38. Switzer JA, Hess DC, Nichols FT, Adams RJ. Pathophysiology and treatment of stroke in sickle-cell disease: present and future Lancet Neurol. 2006 Jun;5(6):501-12.
39. Old J. Hemoglobinopathies and thalassemias. In: Rimoin DL, Connor JM, Pyeritz RE, Korf BR, editors. Emery and Rimoin's principles and practice of medical genetics, 4th ed. London: Churchill Livingstone; 2002. p. 1861–98 [Chapter 68].
40. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998 Jan 1;91(1):288-94.
41. Stockman JA, Nigro MA, Mishkin MM, Oski FA. Occlusion of large cerebral vessels in sickle-cell anemia. N Engl J Med. 1972 Oct 26;287(17):846-9.
42. Pavlakis SG, Bello J, Prohovnik I, Sutton M, Ince C, Mohr JP, Piomelli S, Hilal S, De Vivo DC. Brain infarction in sickle cell anemia: magnetic resonance imaging correlates. Ann Neurol. 1988 Feb;23(2):125-30. 43. Schatz J, White DA, Moinuddin A, Armstrong M, DeBaun MR. Lesion burden and cognitive morbidity in children with sickle cell disease. J Child Neurol 2002;17:891–895.
44. Hebbel RP, Osarogiagbon R, Kaul D. The endothelial biology of sickle cell disease: inflammation and a chronic vasculopathy. Microcirculation. 2004 Mar;11(2):129-51.
45. Driscoll MC, Hurlet A, Styles L, McKie V, Files B, Olivieri N, Pegelow C, Berman B, Drachtman R, Patel K, Brambilla D. Stroke risk in siblings with sickle cell anemia. Blood. 2003 Mar 15;101(6):2401-4.
46. Sebastiani P, Ramoni MF, Nolan V, Baldwin CT, Steinberg MH. Stroke risk in siblings with sickle cell anemia. Blood. 2003 Mar 15;101(6):2401-4.
47. Steinberg MH, Adewoye AH. Modifier genes and sickle cell anemia. Curr Opin Hematol. 2006 May;13(3):131-6.
48. Taylor JG, Tang DC, Savage SA, et al. Variants in the VCAM1 gene and risk for symptomatic stroke in sickle cell disease. Blood. 2002;100:4303–9.
49. Hoppe C, Klitz W, Cheng S, Apple R, et al Gene interactions and stroke risk in children with sickle cell anemia. Blood. 2004 Mar 15;103(6):2391-6
50. Sebastiani P, Ramoni MF, Nolan V, Baldwin CT, Steinberg MH. Genetic dissection and prognostic modeling of overt stroke in sickle cell anemia. Nat Genet. 2005 Apr;37(4):435-40.
51. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998 Jul 2;339(1):5-11.
52. Mudd SH, Levy HL, Skovby F. Disorders of transulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic basis of inherited disease. New York: McGraw Hill; 1995. p. 1279-327.
53. Kelly PJ, Furie KL, Kistler JP, Barron M, Picard EH, Mandell R, Shih VE. Stroke in young patients with hyperhomocysteinemia due to cystathionine beta-synthase deficiency. Neurology. 2003 Jan 28;60(2):275-9.
54. Hassan A, Hunt BJ, O'Sullivan M, Bell R, D'Souza R, Jeffery S, Bamford JM, Markus HS. Homocysteine is a risk factor for cerebral small vessel disease, acting via endothelial dysfunction. Brain. 2004; 127: 212–219.
55. Bellamy MF, McDowell IFW. Putative mechanisms for vascular damage by homocysteine. J Inherit Metab Dis. 1997;20:307–315.
56. Mandel H, Brenner B, Berant M, Rosenberg N, Lanir N, Jakobs C, Fowler B, Seligsohn U. Coexistence of hereditary homocystinuria and factor V Leiden--effect on thrombosis. N Engl J Med. 1996;334(12):763-8.
57. Yap S, Boers GH, Wilcken B, Wilcken DE, Brenton DP, Lee PJ, Walter JH, Howard PM, Naughten ER. Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically: a multicenter observational study. Arterioscler Thromb Vasc Biol. 2001 Dec;21(12):2080-5.
58. Kraus JP1, Janosík M, Kozich V, Mandell R, et al Cystathionine beta-synthase mutations in homocystinuria. Hum Mutat. 1999;13(5):362-75.
59. G Sebastio, M P Sperandeo, M Panico, R de Franchis, J P Kraus, G Andria The molecular basis of homocystinuria due to cystathionine beta-synthase deficiency in Italian families, and report of four novel mutations. Am J Hum Genet. 1995; 56(6): 1324–1333.