Published in final edited form as:
Dev Sci. 2006 July ; 9(4): 411–427.

Hypoxic adaptation during development: relation to pattern of neurological presentation and cognitive disability

Fenella J. Kirkham[1,2,3] and **Avijit K. Datta**[4,5]

1 *Department of Child Health, Southampton University Hospitals NHS Trust, Southampton, UK*

2 *Division of Clinical Neurosciences, University of Southampton, UK*

3 *Neurosciences Unit, Institute of Child Health, University College London, UK*

4 *Institute of Biomedical and Biomolecular Sciences, University of Portsmouth, UK*

5 *Portsmouth Hospitals NHS Trust, Portsmouth, UK*

Abstract

Children with acute hypoxic-ischaemic events (e.g. stroke) and chronic neurological conditions associated with hypoxia frequently present to paediatric neurologists. Failure to adapt to hypoxia may be a common pathophysiological pathway linking a number of other conditions of childhood with cognitive deficit. There is evidence that congenital cardiac disease, asthma and sleep disordered breathing, for example, are associated with cognitive deficit, but little is known about the mechanism and whether there is any structural change. This review describes what is known about how the brain reacts and adapts to hypoxia, focusing on epilepsy and sickle cell disease (SCD). We prospectively recorded overnight oxyhaemoglobin saturation (SpO_2) in 18 children with intractable epilepsy, six of whom were currently or recently in minor status (MS). Children with MS were more likely to have an abnormal sleep study defined as either mean baseline SpO_2 <94% or >4 dips of >4% in SpO_2/hour ($p = .04$). In our series of prospectively followed patients with SCD who subsequently developed acute neurological symptoms and signs, mean overnight SpO_2 was lower in those with cerebrovascular disease on magnetic resonance angiography (Mann-Whitney, $p = .01$). Acute, intermittent and chronic hypoxia may have detrimental effects on the brain, the clinical manifestations perhaps depending on rapidity of presentation and prior exposure.

Introduction

Paediatric neurologists manage children with a range of conditions associated with hypoxia. Survivors of neonatal asphyxia often have long-term motor and cognitive impairments (de Haan, Wyatt, Roth, Vargha-Khadem, Gadian & Mishkin, 2006, this issue), challenging assumptions about the resistance of the immature brain to hypoxia and the degree to which the otherwise expected plasticity may compensate for early brain damage. Other common conditions of childhood are associated with chronic-intermittent hypoxia of varying severity and an increased prevalence of cognitive and behavioural deficits (Kheirandish & Gozal, 2006; Wray, 2006, this issue). Progressive cerebrovascular disease (CVD) (Hogan, Kirkham, Isaacs, Wade & Vargha-Khadem, 2005) or persisting epilepsy may account for some of the poor outcomes in children initially predicted to do well. Variations in presentation, response to treatment and cognitive outcome may also be related to the nature of the injury (focal or global), the stage of brain development at which injury occurs and any acute or chronic systemic disturbance, such as hypotension or hypoxia. The severity and persistence of neurocognitive

Address for correspondence: Fenella J. Kirkham, Departments of Child Health and Clinical Neurosciences, Southampton University Hospitals Trust, Tremona Road, Southampton SO16 6YD, UK; e-mail: fk@soton.ac.uk

deficit may be determined not only by the extent to which hypoxia depletes the brain's energy reserves, but also by the manner in which the brain *responds* to this challenge.

The aim of this review is to describe what is known about how the brain adapts to hypoxia. Evidence is drawn from animal models and diseases affecting older adults, as well as from studies of populations living at altitude. These mechanisms are subsequently explored in the context of epilepsy and of sickle cell disease, an anaemia associated with oxyhaemoglobin desaturation (Setty, Stuart, Dampier, Brodecki & Allen, 2003), subtle white matter abnormality in the absence of brain infarct and intellectual deficit (Baldeweg, Hogan, Saunders, Telfer, Gadian, Vargha-Khadem & Kirkham, 2006;Schatz & Buzan, 2006).

Mechanisms of adaptation to hypoxia

Cognitive effects of acute hypoxia have been likened to alcohol intoxication (Barcroft, 1920), with headache, mental confusion, drowsiness, muscular weakness, inco-ordination and visual disturbance (McFarland & Evans, 1939). Long-term adaptation to intermittent and sustained hypoxia (see Figure 1) may play a role in modifying the effect of acute hypoxia on neurones, reducing the clinically detectable effects (Miyamoto & Auer, 2000). Altitude studies have identified alternative, parallel or serial adaptive mechanisms (Figure 1), including increased erythropoiesis (Dill, 1964), changes in chemosensitive drive to respiration (Fatemian, Gamboa, Leon-Velarde, Rivera-Ch, Palacios & Robbins, 2003), remodelling of the vasculature (Ng, Tan, Ng & Lim, 2005), upregulation of sympathetic mechanisms (Calbet, 2003) and increased exhaled nitric oxide (NO) protecting against hypoxic pulmonary vasoconstriction and improving oxygen transfer in the lung (Beall, Laskowski, Strohl, Soria, Villena, Vargas, Alarcon, Gonzales & Erzurum, 2001). Some genes upregulated during severe ischaemia, are downregulated by a less severe 'preconditioning' insult associated with amelioration of the effects of hypoxia (Figure 1;Stenzel-Poore, Stevens, Xiong, Lessov, Harrington, Mori, Meller, Rosenzweig, Tobar, Shaw, Chu & Simon, 2003).

Recent evidence suggests a key role in acclimatization to chronic hypoxaemia for Hypoxia-Inducible Factor (HIF) stabilization which upregulates endothelin, erythropoietin and growth factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PGF) (Figure 1) (Semenza, 2001). Erythropoietin is neuroprotective (Chang, Mu, Wendland, Sheldon, Vexler, McQuillen & Ferriero, 2005), as well as increasing red cell mass and oxygen carrying capacity. HIF stabilization also improves host defence in response to infection (Peyssonnaux, Datta, Cramer, Doedens, Theodorakis, Gallo, Hurtado-Ziola, Nizet & Johnson, 2005) and heat acclimatization (Shein, Horowitz, Alexandrovich, Tsenter & Shohami, 2005), providing a basis for interactions between adaptations (Datta & Tipton, 2006) of relevance to children.

Upregulation of gene products by hypoxia may be age-dependent. As well as inducing angiogenesis, VEGF may induce vascular leakage leading to cerebral oedema (Schoch, Fischer & Marti, 2002) at altitude (Tissot van Patot, Leadbetter, Keyes, Bendrick-Peart, Beckey, Christians & Hackett, 2005) and after status epilepticus (Croll, Goodman & Scharfman, 2004). There are age differences in VEGF expression of potential physiological importance; in the systemic circulation (Rivard, Berthou-Soulie & Principe, 2001) and carotid body (Di Giulio, Bianchi, Cacchio, Artese, Rapino, Macri & Di Ilio, 2005) it is greater in the young with evidence for neuroprotection. HIF stabilization appears to be associated with more apoptotic cell death in older animals (Rapino, Bianchi, Di Giulio, Centurione, Cacchio, Antonucci & Cataldi, 2005); in this age group, lack of expression is neuroprotective (Helton, Cui, Scheel, Ellison, Ames, Gibson, Blouw, Ouyang, Dragatsis, Zeitlin, Johnson, Lipton & Barlow, 2005). Certain polymorphisms increase susceptibility to Alzheimer's, again suggesting an important role for VEGF in neuroprotection (Del Bo, Scarlato, Ghezzi, Martinelli Boneschi,

Fenoglio, Galbiati, Virgilio, Galimberti, Galimberti, Crimi, Ferrarese, Scarpini, Bresolin & Comi, 2005).

Hypoxic induction of NO synthesis is important because NO has a role in HIF stabilization (Hagen, Taylor, Lam & Moncada, 2003) and is a powerful vasodilator increasing tissue oxygen delivery (Bertuglia & Giusti, 2005), although there is ongoing controversy about the precise mechanism. One group has provided evidence that haemoglobin reduces nitrite (Figure 1), releasing NO during haem deoxygenation, with maximal activity observed at 50% haemoglobin oxygenation (P_{50}), stimulating vasodilatation (Crawford, Isbell, Huang, Shiva, Chacko, Schechter, Darley-Usmar, Kerby, Lang, Kraus, Ho, Gladwin & Patel, 2005). Another has shown that during oxygen binding to haem as blood is oxygenated in the lungs, NO binding to a cysteine on the haemoglobin molecule forming S-nitrosylated haemoglobin (SNO) (Figure 1), which changes from the vasoconstricting R state to the vasodilating T state upon deoxygenation, releasing the NO locally (Stamler, Jia, Eu, McMahon, Demchenko, Bonaventura, Gernert & Piantadosi, 1997). Haemoglobin therefore appears to play a key role in matching tissue perfusion to oxygen demand by reacting with nitrite (Gladwin, Crawford & Patel, 2004) or SNO (Singel & Stamler, 2005) (Figure 1) in a manner allosterically regulated by oxygen tension. Central neural transduction of the hypoxic ventilatory response appears to depend on signalling in the brainstem by reactive S-nitrosylated (SNO) molecules, such as S-nitrosoglutathione, formed locally when the NO released from deoxygenated SNO-haemoglobin binds (Lipton, Johnson, Macdonald, Lieberman, Gozal & Gaston, 2001).

The incidence and extent of neurocognitive deficit in children living at altitude is unknown, but these children provide an important naturalistic model for hypoxic-adaptation of relevance to other populations (Virués-Ortega, Garrido, Javierre & Kloezeman, 2006, this issue). For example, the hyperventilatory response (Figure 1), well recognized at altitude, may be particularly important in anaemia, where oxygen delivery may be maintained by increased cardiac output or tissue oxygen extraction (Macarlupu, Buvry, Morel, Leon-Velarde, Richalet & Favret, 2006). In populations native to high altitude, there are at least three distinct phenotypes: Andeans, Ethiopians and Tibetans (Beall, 2000a;Beall *et al.*, 2001), which might represent differences in distribution of genetic polymorphisms, although this awaits confirmation (Mejia, Prchal, Leon-Velarde, Hurtado & Stockton, 2005). Mechanisms of adaptation include: erythropoiesis, enlarged chests and a blunted ventilatory response to hypoxia reducing the work of breathing (Andeans); increased NO production (Tibetans); and hyper-ventilation (Ethiopians) (Beall, 2003). Data in those of African origin are limited but oxyhaemoglobin saturation (SpO_2) is relatively normal in Ethiopians living at high altitude (Beall, Decker, Brittenham, Kushner, Gebremedhin & Strohl, 2002) while at lower altitude, tidal volume is reduced, respiratory rate increased and SpO_2 lower in the Xhosa than in Caucasians (Terblanche, Tolley, Fahlman, Myburgh & Jackson, 2005). In young adult African Americans, peripheral chemosensitivity is increased during sleep, although baroreceptor responses are reduced compared with Caucasians (Crisostomo, Zayyad, Carley, Abubaker, Onal, Stepanski, Lopata & Basner, 1998), perhaps providing a basis for variation in prevalence of chronic hypertension. These differences may reflect subtle variations in earlier exposure to hypoxia rather than, or as well as, natural selection for genetic polymorphisms (Terblanche *et al.*, 2005).

Adaptations prior to conception, during foetal life and in early childhood (Beall, 2000b) may play an important role. Age-dependent chronic adaptations include attenuation of hypoxic hyperventilatory response after exposure to intermittent hypoxia (Gozal & Gozal, 2001), the degree of alveolar branching (van Tuyl, Liu, Wang, Kuliszewski, Tibboel & Post, 2005), increases in cerebral capillary density (LaManna, Chavez & Pichiule, 2004), size and shape of cerebral smooth muscle and endothelial cells (Williams & Pearce, 2005) and response to sympathetic stimulation and calcium-dependent and -independent mechanisms for smooth

muscle contraction (Longo & Pearce, 2005). If a hypoxic challenge occurs later in life, any of these prior adaptations might determine the mechanisms available to respond, and the nature of any sequelae if the response is inadequate.

Adaptation to intermittent or sustained hypoxia might particularly determine the type of neurological complications for which patients are at risk when exposed to acute hypoxia. For example, persistently low levels of tissue oxygen in anaemia may lead to neuroprotective erythropoietin production, but release of younger, more adhesive red cells and any associated haemolysis (Rice & Alfrey, 2005) may adversely affect endothelial function (Gladwin & Kato, 2005), eventually leading to irreversible vascular disease. Erythropoietic changes in skull thickness and facial bone morphology potentially reduce airway size and lead to intermittent hypoxaemia. In obstructive sleep apnoea, upregulation of inflammatory proteins adversely affects endothelial function, leading to reduced arterial diameter (Minoguchi, Yokoe, Tazaki, Minoguchi, Tanaka, Oda, Okada, Ohta, Naito & Adachi, 2005); high middle cerebral artery velocities have also been demonstrated in children with primary snoring (Hill, Hogan, Onugha, Harrison, Cooper, McGrigor, Datta & Kirkham, 2006). Interestingly, patients with Parkinson's disease (Onodera, Okabe, Kikuchi, Tsuda & Itoyama, 2000) have impaired chemosensitivity to hypoxia. In the elderly, oxyhaemoglobin desaturation is associated with periventricular white matter lesions on MRI (van Dijk, Vermeer, de Groot, van de Minkelis, Prins, Oudkerk, Hofman, Koudstaal & Breteler, 2004).

In summary, there are a number of adaptations to hypoxia, which may depend on genetic factors and on the timing, degree and duration of exposure. The effect of these variables in individuals and the specific consequences in terms of cerebrovascular pathology and neurological disease remain to be determined now that population-based normal data are available (Urschitz, Wolff, Von Einem, Urschitz-Duprat, Schlaud & Poets, 2003).

Exposure to hypoxia in a common neurological disease of childhood: epilepsy

Some childhood epilepsies are recognized by paediatric neurologists as 'malignant' in that seizures are frequent and resistant to medication and the child's development arrests (Dulac & Chiron, 1996;Drury, 2002). Aetiology is obscure in many cases, although some patients have a gene coding for an abnormal component of an ion channel and others may have focal or generalized structural abnormality; children with Sturge-Weber syndrome (see Figure 2) may follow this course (Maria, Neufeld, Rosainz, Drane, Quisling, Ben-David & Hamed, 1998). Many children spend prolonged periods of time in 'minor status' (MS), a state of clouded consciousness with frequent absences and sometimes drop attacks, accompanied by continuous discharges on the EEG (Brett, 1966;Drury, 2002).

Hypoxia appears to exacerbate seizures in 10-day-old, but not older or younger rats (Jensen, Holmes, Lombroso, Blume & Firkusny, 1992), suggesting an age-dependent effect. There are chronic abnormalities of cerebral perfusion and metabolism detectable with diffusion (Figure 2) and perfusion MRI or positron emission tomography (PET) (Ferrie, Maisey, Cox, Polkey, Barrington, Panayiotopoulos & Robinson, 1996), which might interact with chronic hypoxaemia in the maintenance of epileptogenicity. Vasculopathy may play a role in some cases (Pascual-Castroviejo, Lopez Martin, Martinez Bermejo & Perez Higueras, 1994). Seizures are usually accompanied by an increase in CBF to meet increased metabolic demand (Brodersen, Paulson, Bolwig, Rogon, Rafaelsen & Lassen, 1973) but not in patients with Sturge-Weber syndrome, rendering them vulnerable to ictal ischaemia (Aylett, Neville, Cross, Boyd, Chong & Kirkham, 1999). Sleep disordered breathing (SDB) and intermittent or sustained oxyhaemoglobin desaturation might contribute to intractability in epilepsy. Abnormal polysomnography has been documented (Malow, Levy, Maturen & Bowes,

2000;Koh, Ward, Lin & Chen, 2000), and appropriate treatment, e.g. adenotonsillectomy or continuous positive airway pressure (CPAP), has been associated with reduction in seizure frequency (Cohen, Lefaivre, Burstein, Simms, Kattos, Scott, Montgomery & Graham, 1997; Holland & Yan, 1997).

We prospectively recorded overnight SpO_2 in 18 children with intractable epilepsy, six of whom were currently or recently in MS. An abnormal study was defined as either: (a) mean baseline SpO_2 <94%; or, (b) >4 dips of >4% in SpO_2/hour. Children with MS were more likely to have an abnormal sleep study ($p = .04$) and had more dips/hour ($p = .04$). There was a trend for minimum SpO_2 to be lower in those with MS ($p = .06$) but there was no difference in mean SpO_2 between those with and without MS ($p = .6$). Although it is possible that abnormal sleep studies were directly related to frequent seizures in children with MS, there may be a self-feeding loop such that SDB and nocturnal hypoxaemia in turn contribute to intractability and to cognitive deterioration in epileptic children. The possibility that such a vicious cycle contributes to progressive brain damage could be explored in populations such as those with Sturge-Weber syndrome (Figure 2). Prospective research is needed to understand mechanisms and test therapies.

Exposure and adaptation to hypoxia in a common haemoglobinopathy of childhood: sickle cell disease

Sickle oxyhaemoglobin has a reduced affinity, i.e. the partial pressure of oxygen (PaO_2) at which haemoglobin is 50% saturated (P_{50}) is increased, although there is considerable variation between patients (Rackoff, Kunkel, Silber, Asakura & Ohene-Frempong, 1993). Thus arterial blood has lower oxygen saturation for any given arterial PaO_2; this has advantages and disadvantages, which may depend on degree of hypoxic exposure (Samaja, Crespi, Guazzi & Vandegriff, 2003). Unloading of oxygen from blood to tissues is facilitated (lessening the drive for chronic adaptative gene upregulation), but oxygen loading at the lungs is reduced. As foetal haemoglobin levels fall during childhood, oxyhaemoglobin affinity must drop, although there are few data on time course. This may influence the hypoxic response and alter cerebral oxygen extraction, as has been suggested for altitude sickness in the general population (Curran-Everett, 2003).

Daytime SpO_2 measured using pulse oximetry is low in many SCD patients, in association with degree of anaemia and increasing age (Rackoff *et al.*, 1993), although because of reduced oxygen affinity, arterial hypoxaemia is rarely demonstrated. Overnight oxyhaemoglobin desaturation (Kirkham, Hewes, Prengler, Wade, Lane & Evans, 2001a;Setty *et al.*, 2003) and SDB, usually accompanied by snoring, are common (Samuels, Stebbens, Davies, Picton-Jones & Southall, 1992). Acute chest syndrome (ACS), defined as acute respiratory symptoms accompanied by new lung abnormalities on chest X-ray (Vichinsky, Neumayr, Earles, Williams, Lennette, Dean, Nicherson, Orringer, McKie, Bellevue, Daeschner & Manci, 2000) and acute exposure to altitude (Green, Huntsman & Serjeant, 1971) may be associated with severe acute hypoxaemia. Both low (Fowler, Smith & Greenfield, 1957) and high blood carbon dioxide (Maddern, Reed, Ohene-Frempong & Beckerman, 1989) have been documented, the former probably secondary to an increased hypoxic hyperventilatory response and the latter suggestive of nocturnal hypoventilation, potentially protective as cerebral blood flow (CBF) and oxygen delivery may increase.

Hypoxia-reoxygenation in SCD is characterized by inflammation with upregulation of xanthine oxidase, superoxide generation, oxidative stress and increased monocyte tissue factor (Kaul & Hebbel, 2000) (Figure 1). Although endothelial NO synthase (eNOS) is upregulated, NO is scavenged by superoxide as well as free haemoglobin, released by chronic haemolysis (Reiter, Wang, Tanus-Santos, Hogg, Cannon, Schechter & Gladwin, 2002); bioavailablity is

less during acute complications, including chest crisis. Potentially protective interactions, e.g. heat shock protein 90 with eNOS, may be limited, in association with oxidative stress. Circulating endothelin-1, a peptide with vasoconstrictor and bronchoconstrictor effects, is inversely correlated with daytime SpO_2 in SCD (Werdehoff, Moore, Hoff, Fillingim & Hackman, 1998); vascular tone may be delicately balanced depending on NO availability (Pluta, Dejam, Grimes, Gladwin & Oldfield, 2005) and endothelin levels (Figure 1). Rapid polymerization of HbS and relative deficiency of SNO (Pawloski, Hess & Stamler, 2005) during acute hypoxia also appears to interfere with red cell oxygen sensing and hypoxic vasodilatation. Hypoxia also increases adhesion of sickle red cells to endothelial wall via mechanisms that include vascular cell adhesion molecule (VCAM-1) and P-selectin (Setty *et al.*, 2003); levels are increased when NO bioavailability is reduced. The challenge is to translate these scientific advances to tackle problems facing clinicians caring for SCD patients with acute or chronic intermittent or sustained hypoxia.

Neurologically asymptomatic SCD patients usually have *globally* high CBF secondary to anaemia (Herold, Brozovic, Gibbs, Lammertsma, Leenders, Carr, Fleming & Jones, 1986;Prohovnik, Pavlakis, Piomelli, Bello, Mohr, Hilal & De Vivo, 1989), which means that the capacity to respond to other vasodilatory stimuli, e.g. blood carbon dioxide, may be reduced. However, in symptomatic patients diffusely decreased cerebral perfusion is typical (Huttenlocher, Moohr, Johns & Brown, 1984). Studies of *regional* CBF, using xenon-CT or PET have shown more extensive regional perfusion abnormalities than those shown on anatomical CT or MRI (Numaguchi, Haller, Humbert, Robinson, Lindstrom, Gruenauer & Carey, 1990;Powars, Conti, Wong, Groncy, Hyman, Smith, Ewing, Keenan, Zee, Harold, Hiti, Teng & Chan, 1999). Symptomatic patients with vessel occlusion have reduced CBF distally in the acute phase (Huttenlocher *et al.*, 1984) and chronically (Powars *et al.*, 1999;Kirkham, Calamante, Bynevelt, Gadian, Cox, Evans & Connelly, 2001b;Prengler, Pavlakis, Boyd, Connelly, Calamante, Chong, Saunders, Cox, Bynevelt, Lane, Laverty & Kirkham, 2005). Some patients with normal MRA have CBF reduction focally, particularly posteriorly (Kirkham *et al.*, 2001b).

CBF in SCD appears to depend on bioavailability of endothelial NO (French, Kenny, Scott, Hoffmann, Wood, Hudetz & Hillery, 1997), which may be close to a critically low threshold because it is scavenged (Morris, Kato, Poljakovic, Wang, Blackwelder, Sachdev, Hazen, Vichinsky, Morris & Gladwin, 2005). Dietary supplementation of arginine, an amino acid precursor of NO, may improve endogenous NO bioavailability and performance of motor coordination tasks such as the rotorod in animals (Fasipe, Ubawike, Eva & Fabry, 2004) as well as improving cerebral perfusion and reducing red cell density and mean cell haemoglobin concentration (Romero, Suzuka, Nagel & Fabry, 2002;Kennan, Suzuka, Nagel & Fabry, 2003;Fabry, Etzion, Bookchin, Suzuka & Nagel, 2004).

There are differences in cerebral haemodynamics in response to vasodilatory stimuli in SCD: acetazolamide increases CBF in normal adults but the response was reduced in two-thirds of SCD patients (Kedar, Drane, Shaeffer, Nicole & Adams, 2006). Although there are few formal data on carbon dioxide reactivity, hyper-ventilation may reduce CBF and precipitate posterior circulation infarction (Protass, 1973;Allen, Imbus, Powars & Haywood, 1976;Arnow, Panwalker, Garvin & Rodriguez-Erdmann, 1978). Cerebral oxygen saturation is reduced in patients with SCD compared with controls and falls further during sleep (Nahavandi, Tavakkoli, Hasan, Wyche & Castro, 2004;Raj, Bertolone, Mangold & Edmonds, 2004;Raj, O'Brien, Edmonds, Bertolone & Gozal, 2005). Whereas high oxygen tension reduces CBF in control animals, baseline CBF is decreased in transgenic sickle mice compared with controls and increases with hyperoxia in mice (Kennan, Suzuka, Nagel & Fabry, 2004) and patients (Kennan, Suzuka, Nagel & Fabry, 2002) with SCD. CBF velocity and cerebral oxygenation increase rapidly after blood transfusion (Venketasubramanian, Prohovnik, Hurlet, Mohr &

Piomelli, 1994;Nahavandi *et al.*, 2004;Raj *et al.*, 2004). In one patient transfused after stroke, CBF increased immediately after Nifedipine (Ashwal, Bedros & Thompson, 1994) while both increases and decreases have been documented in humans and animals without SCD, perhaps dependent on the resting blood pressure (Grabowski & Johansson, 1985). Blood oxygen level-dependent (BOLD) MRI or transcranial Doppler (TCD) techniques could be employed to explore the relationship between hypoxia, hypercapnia and CBF regulation and to test novel therapies in humans in parallel with carefully designed neuropsychological paradigms and neurological examination (Kennan *et al.*, 2004;Rostrup, Larsson, Born, Knudsen & Paulson, 2005;Hill *et al.*, 2006).

Erythropoetin levels are raised in patients with SCD (Figure 1), but relatively less than in other patients with alternative causes for a comparable anaemia (Sherwood, Goldwasser, Chilcote, Carmichael & Nagel, 1986), probably related to oxyhaemoglobin affinity. VEGF and PGF are raised in SCD (Solovey, Gui, Ramakrishnan, Steinberg & Hebbel, 1999;Gurkan, Tanriverdi & Baslamisli, 2004;Perelman, Selvaraj, Batra, Luck, Erdreich-Epstein, Coates, Kalra & Malik, 2003). PGF levels are higher in those with frequent pain, associated with monocyte activation (Perelman *et al.*, 2003), which is inversely related to overnight hypoxia (Inwald, Kirkham, Peters, Lane, Wade, Evans & Klein, 2000). Haemoxygenase is upregulated and may be protective via antioxidant effects of bilirubin and vasodilatory effects of carbon monoxide (Jison, Munson, Barb, Suffredini, Talwar, Logun, Raghavachari, Beigel, Shelhamer, Danner & Gladwin, 2004), demonstrable by increased plasma carboxyhaemoglobin and exhaled carbon monoxide (Cunnington, Kendrick, Wamola, Lowe & Newton, 2004;Sylvester, Patey, Rafferty, Rees, Thein & Greenough, 2005) and reduced P_{50} (Figure 1). However, haemoxygenase also upregulates VEGF, leading to a potentially deleterious cycle of angiogenesis (Bussolati, Ahmed, Pemberton, Landis, Di Carlo, Haskard & Mason, 2004).

Angiographic evidence of large vessel occlusion in the majority of sickle-associated strokes (Stockman, Nigro, Mishkin & Oski, 1972) has led to non-invasive population screening with TCD to detect CVD (Adams, McKie, Carl, Nichols, Perry, Brock, McKie, Figueroa, Litaker, Weiner & Brambilla, 1997), an approach founded on significant impact from transfusion programmes on stroke incidence and recurrence (Fullerton, Adams, Zhao & Johnston, 2004). Vasculopathy starts young: high TCD velocities occur in infancy (Hogan, Kirkham, Prengler, Telfer, Lane, Vargha-Khadem & de Haan, 2005) and abnormal MRAs have been demonstrated by the second year (Wang, Langston, Steen, Wynn, Mulhern, Wilimas, Kim & Figueroa, 1998).

As well as anaemia-related increased CBF, high CBFV may reflect vasoconstriction, perhaps secondary to imbalance between endothelin production and NO availability, which might protect against development of cerebral oedema on exposure to acute hypoxia at the cost of increasing ischaemic risk in the territory of the affected arteries. There may be an important interaction between exposure to hypoxia, haemolysis, infection and inflammation in determining whether a vessel previously in (adaptive) spasm (Hill *et al*., 2006) becomes irreversibly stenosed or occluded. Mechanisms related to hypoxic exposure potentially favouring the development of irreversible CVD include unregulated angiogenesis, thrombosis and endothelial adhesion. There is some evidence for this: for example, intermittent hypoxia and infection increases haemolysis, platelet and white cell activation and endothelial adhesion in SCD (Inwald *et al.*, 2000;Setty *et al.*, 2003). If this is important clinically, an association between SpO_2, haemolysis, and severity of vasculopathy might be expected.

In our series of prospectively followed patients with SCD, screened at baseline with TCD, overnight pulse oximetry (Table 2) and MRI and MRA if they were >7 years old, who subsequently developed acute neurological symptoms and signs (Kirkham *et al.*, 2001a,Tables 2 and 3), mean overnight SpO_2 was lower and mean reticulocytes higher in those with CVD

on MRA (Mann-Whitney, $p < .01$ for both). All seven with an abnormal sleep study had an abnormal MRA (Table 2) while five children in this series who had normal MRA all had a normal sleep study (prospectively defined as mean SpO_2 >92% and no dips). None of the latter group presented with hemiparesis or had infarction in an arterial distribution (Table 3) but three had episodes of dizziness with or without paraesthesiae or confusion compatible with posterior transient ischaemic attacks, one of whom subsequently presented with an organic psychosis (Table 3). Another had a venous sinus thrombosis (Sébire, Tabarki, Saunders, Leroy, Liesner, Saint-Martin, Husson, Williams & Kirkham, 2005). The case history of the remaining patient, who had bilateral borderzone infarction, is given in the legend to Figure 3. These presentations are similar to those documented at altitude (Basnyat, Wu & Gertsch, 2004) and are compatible with the effects of acute hypoxia without prior preconditioning exposure or perhaps with acutely low blood carbon dioxide levels and vasoconstriction. The majority of patients had homozygous sickle cell anaemia (Table 2) but there was no obvious threshold of haemoglobin or haemoglobin F (Powars, Weiss, Chan & Schroeder, 1984) predictive of neurological manifestations and only two patients had ICA/MCA velocities >200 cm/sec (Adams *et al.*, 1997) at any stage. Thirteen patients had recurrent neurological events, which occurred in those who had had a prodromal illness at the time of the index event and in those who had not (Table 3).

ACS is associated with acute hypoxia and relative anaemia (haemoglobin falling at least 1 g/dl from baseline; Henderson, Noetzel, McKinstry, White, Armstrong & DeBaun, 2003). In one series, 3% of ACS patients had neurological symptoms at presentation and 7–10% as a complication (Figure 5;Vichinsky *et al.*, 2000). Brain imaging findings include posterior leukoencephalopathy, bilateral focal cortical oedema, haemorrhage and acute demyelination (Henderson *et al.*, 2003;Lee, McKie, Sekul, Adams & Nichols, 2002). Asthma may be a risk factor for both (Nordness, Lynn, Zacharisen, Scott & Kelly, 2005). Reversibility of the majority of imaging abnormalities and white matter involvement is reminiscent of high altitude cerebral oedema (HACE), venous sinus thrombosis and other neurological syndromes seen in unacclimatized adults who climb mountains quickly and are therefore exposed to acute hypoxia without adequate preconditioning (Kobayashi, Koyama, Kubo, Fukushima & Kusama, 1987;Hackett, Yarnell, Hill, Reynard, Heit & McCormick, 1998;Saito & Tanaka, 2003;Basnyat *et al.*, 2004). Lesion distribution may be different although there are very few imaging data in children with HACE for comparison. Age, rapidity and severity of hypoxia, nature and degree of any adaptive preconditioning or associated pre-existing CVD might influence outcome (Figure 1). The preconditioning effects of chronic hypoxia might lead to relatively small areas of infarction after acute hypoxic exposure compared with the degree of vasculopathy (Figure 4). Oedema might be expected in territories distal to normal (rather than stenosed) vessels in patients who are exposed to acute hypoxia from a normal baseline, i.e. without preconditioning (Figures 3 and 5).

Although few patients have chronic epilepsy, partial or generalized seizures affect 13% of SCD patients, herald stroke in 10–33% (Liu, Gzesh & Ballas, 1994) and are a risk factor for silent infarction (Kinney, Sleeper, Wang, Zimmerman, Pegelow, Ohene-Frempong, Wethers, Bello, Vichinsky, Moser, Gallagher, DeBaun, Platt & Miller, 1999). Abnormalities of TCD and MR perfusion are commoner in patients with active seizures (Prengler *et al.*, 2005). Rapid change in tissue oxygenation might lead to changes in ion channel function leading to isolated seizures, which might not recur once hypoxic adaptation has occurred, or occasionally to structural damage to the hippocampus and chronic epilepsy (Figure 5). Headache, common in SCD (Palermo, Platt-Houston, Kiska & Berman, 2005) is also seen at altitude (Jaillard, Mazetti & Kala, 1997), apparently in association with oxyhaemoglobin desaturation despite relative polycythaemia (Arregui, Leon-Velarde, Cabrera, Paredes, Vizcarra & Umeres, 1994). Pseudotumour cerebri has been reported in SCD (Henry, Driscoll, Miller, Chang & Minniti, 2004) as well as OSA in adults (Wolin & Brannon, 1995).

Parenchymal and cerebrovascular changes in asymptomatic patients

In addition to infarction visible on CT or MRI (Adams, Nichols, McKie, McKie, Milner & Gammal, 1988;Pavlakis, Bello, Prohovnik, Sutton, Ince, Mohr, Piomelli, Hilal & De Vivo, 1988), there is evidence for subtle abnormality on quantitative T1-weighted MRI, particularly thalamic, in young SCD children (Steen, Langston, Reddick, Ogg, Chen & Wang, 1996). Both increased tortuosity (ectasia) and quantitative T1-weighted MRI changes are related to haematocrit (Steen, Xiong, Mulhern, Langston & Wang, 1999;Steen, Reddick, Glass & Wang, 1998), suggesting that chronic anaemic hypoxia might be an important drive to vascular adaptation with failure to compensate leading to brain pathology.

Possible mechanisms for covert infarction include residua of acute hypoxic posterior leukencephalopathy, cerebral oedema and basal ganglia infarction (Henderson *et al.*, 2003;Usui, Inoue, Kimura, Kirino, Nagaoka, Abe, Nagata & Arai, 2004;Jeong, Kwon, Chin, Yoon & Na, 2002) and venous sinus thrombosis (Sébire *et al.*, 2005) as well as transient ischaemic attack secondary to arterial disease. Patent foramen ovale (PFO) is a well-recognized cause of sustained and intermittent hypoxia common in patients with right ventricular dysfunction, obstructive airways disease and OSA (Shnaider, Shiran & Lorber, 2004;Soliman, Shanoudy, Liu, Russell & Jarmukli, 1999;Shanoudy, Soliman, Raggi, Liu, Russell & Jarmukli, 1998), and is a potentially treatable cause of stroke and migraine in young adults (Finsterer, Sommer, Stiskal, Stollberger & Baumgartner, 2005). However, the possibility that PFO is a risk factor for overt or covert infarction in SCD has received little attention (Dowling, 2005). White matter changes (Baldeweg *et al.*, 2006;Schatz & Buzan, 2006) might also reflect acute reduction in CBF secondary to low blood carbon dioxide levels (Murase & Ishida, 2005) or even local carbon monoxide toxicity (Durak, Coskun, Yikilmaz, Erdogan, Mavili & Guven, 2005) secondary to upregulation of haemoxygenase (Figure 1). Other molecular mechanisms linking chronic sustained and intermittent hypoxia to the neurological manifestations of SCD include the adverse effects of reactive oxygen species generated by repetitive intermittent hypoxia on proteins, nucleic acids and lipids, downregulation of the mitochondrial respiratory chain enzymes and upregulation of amyloid β peptide as well as the effect of sleep disruption (Figure 1).

Implications for future management: strategies to prevent hypoxia-related morbidity

Management strategies to prevent adverse effects of hypoxia on neurocognitive function might include oxygen supplementation for those who are chronically hypoxic, CPAP or surgical approaches, e.g. adenotonsillectomy for OSA. Nutritional supplements, vitamins, e.g. C and E, trace elements, e.g. zinc, and drugs, e.g. aspirin, which are anti-inflammatory, antioxidant and/or increase oxyhaemoglobin affinity might also ameliorate conditions associated with chronic hypoxia, particularly if generation of reactive oxygen species has overwhelmed capacity for compensatory scavenging. To ensure that interventions are appropriate and risk-free, it is important to determine the child's mechanism of hypoxaemic adaptation, using measurement of overnight oximetry, red cell indices, oxyhaemoglobin affinity, carboxyhaemoglobin, blood pressure, peripheral constriction, respiratory function, exhaled NO and hypoxic ventilatory response (Figure 1). Controlled trials of strategies to prevent morbidity and neurocognitive deficits associated with hypoxia are justified, but should be based on detailed understanding of pathophysiology.

Acknowledgements

This work was funded by Action Research, the Wellcome Trust, the National Heart, Blood and Lung Institute of the National Institutes of Health (5-R01-HL079937) and the Stroke Association (PROG4). The work was undertaken at NHS Trusts which receive a proportion of their funding from the NHS Executive.

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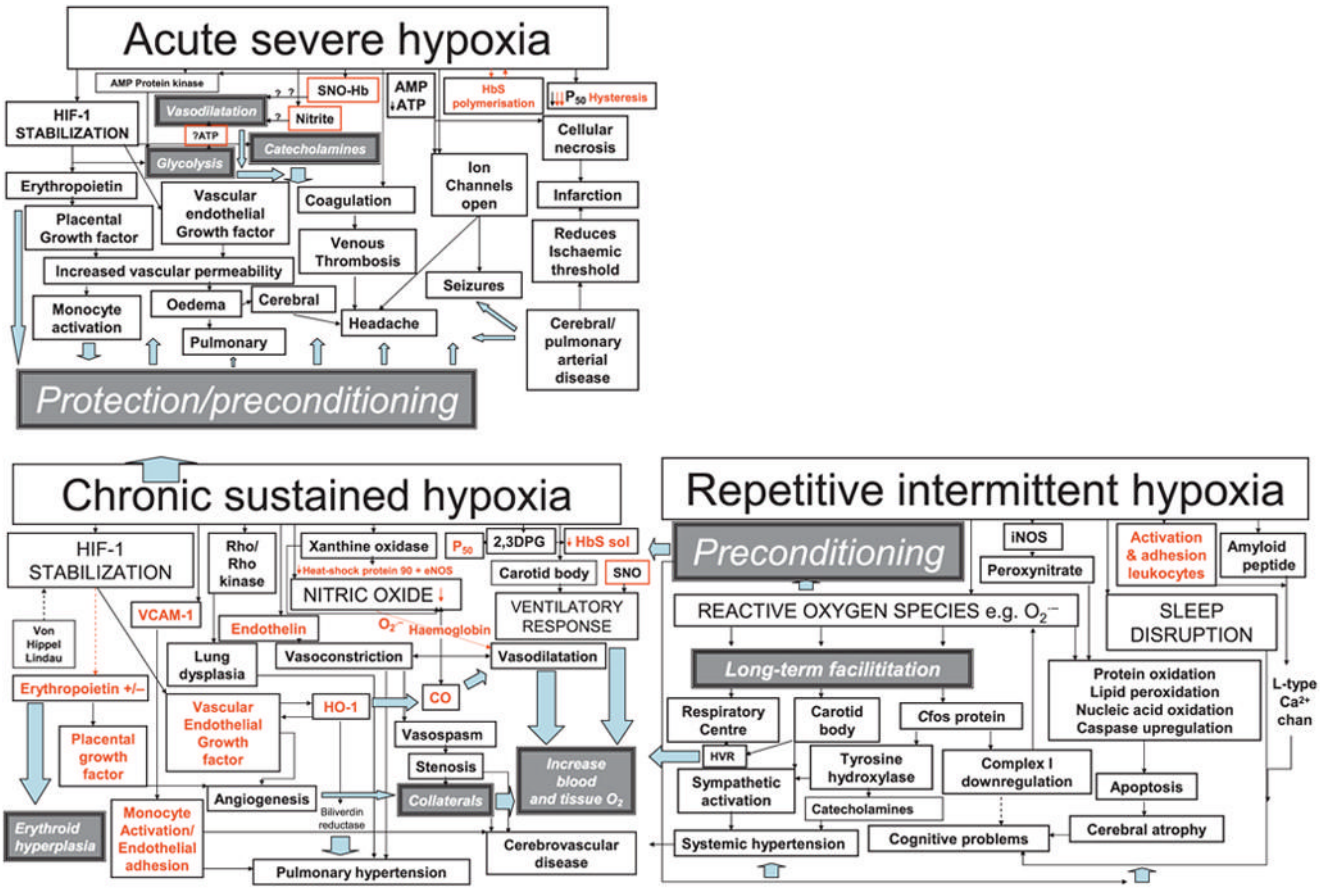

Figure 1.

Clinical features are represented by pale grey boxes while white boxes/black arrows refer to mechanisms likely to lead to pathology (red for those for which there is evidence in sickle cell disease, SCD) and dark grey boxes/pale blue arrows refer to potentially protective mechanisms. Red boxes denote mechanisms involving the red cell postulated to be involved in vasodilatation in response to local hypoxia. In chronic sustained hypoxia, hypoxia-inducible factor stabilization leads to upregulation of erythropoietin and growth factors. In addition, there is increased nitric oxide synthesis, although in SCD free haemoglobin secondary to chronic haemolysis and the superoxide generated by increased xanthine oxidase activity may reduce bioavailability and tip the delicate balance between vasodilatation and vasoconstriction in favour of the latter. Vasconstriction is also favoured by the release of endothelin in response to hypoxia. Increased 2,3 dihydophosphoglycerate (2,3 DPG) further increases P_{50} and decreases Haemoglobin S solubility. Adhesion molecules, such as VCAM-1, are upregulated and favour monocyte adhesion to the endothelium. Upregulation of haem-oxygenase-1 (HO-1) may have protective effects, including vasodilatation and reduction of P_{50} secondary to the generation of carboxyhaemoglobin, and the antioxidant effects of bilirubin reductase, but also further upregulates vascular endothelial growth factor and may increase carbon monoxide levels locally. The ventilatory response may be increased, probably facilitated by repetitive intermittent hypoxia. Cerebral infarction, atrophy and cognitive problems may be related to a number of mechanisms related to chronic sustained and intermittent hypoxia, including perhaps demyelination secondary to chronically high carbon monoxide levels, the adverse effects of reactive oxygen species generated by repetitive intermittent hypoxia on proteins, nucleic acids and lipids, downregulation of the mitochondrial respiratory chain enzymes and upregulation

of amyloid β peptide, as well as the effect of sleep disruption. Chronically hypoxic patients with SCD may be preconditioned and therefore relatively protected from the effects of acute hypoxia, e.g. vasogenic oedema secondary to increased vascular endothelial growth factor, opening of ion channels and venous thrombosis. However, the very rapid polymerization of HbS may cause such severe hypoxia that immediately available compensatory mechanisms, such as increased glycolysis, relative hypertension secondary to catecholamine release, and vasodilatation secondary to release of nitric oxide by S-nitrosylated haemoglobin (SNO-Hb), are overwhelmed and acute neurological complications, such as headache, seizures, cerebral oedema, as well as stroke, are inevitable.

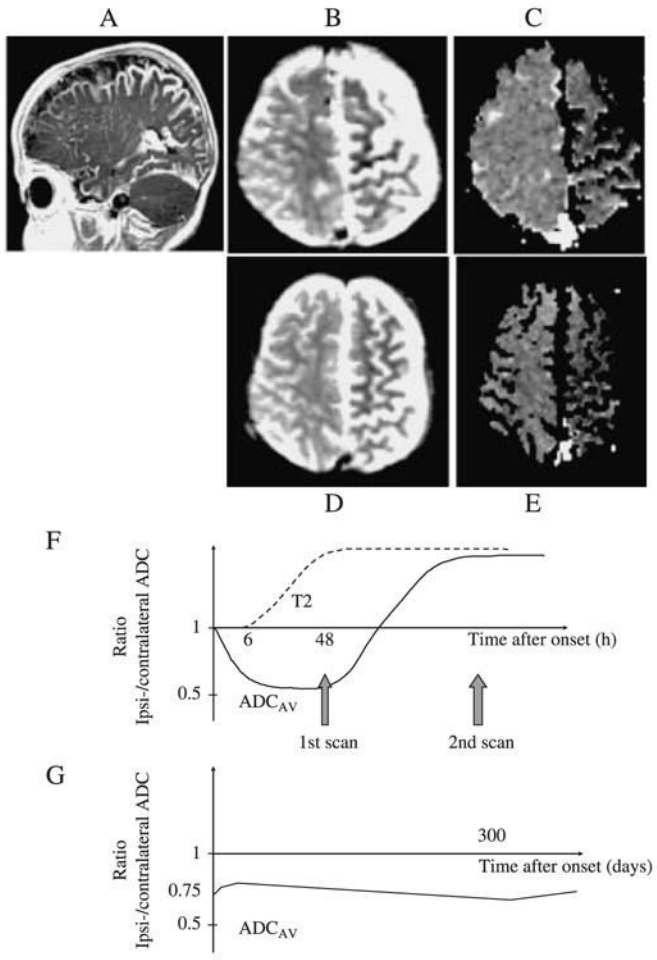

Figure 2.

This patient was born with a left capillary haemangioma in the V1–2 distribution and demonstration of a pial angioma confirmed the diagnosis of Sturge-Weber syndrome. She presented at age 4 months with 6 days of frequent treatment-resistant seizures lasting up to 2 hours. T2-weighted imaging (B) and diffusion imaging (C) were performed 6, 12 and 25 days after initial presentation. The apparent diffusion coefficient (ADC) maps obtained at 6 days after initial onset of the seizures showed evidence of ongoing restricted diffusion throughout a substantial part of the abnormal left hemisphere (C). Representative regions showed an ipsi/contralateral ADC ratio of 0.79 (shown graphically in G, compared with values of the order of 0.5 in the first 48 hours in a child with a stroke and 1.0 in controls, shown graphically in F). The ADC remained low in the affected areas at 12 and 25 days after presentation (shown graphically in G, ipsi/contralateral ADC ratio 0.81 and 0.84 respectively). Throughout this period, the T2-weighted images showed hypointensity in corresponding regions. The patient developed a right hemiparesis and chronic epilepsy. A sleep study showed mean and minimum oxyhaemoglobin saturation (SpO_2) of 95.8% and 91% respectively (97% is the 5th percentile in normal children; Urschitz *et al.*, 2003). A follow-up scan was performed at the age of 14 months (D, E); the ADC remained low with an ipsi/contralateral ADC ratio of 0.79 (shown graphically in G). At the age of 15 months, her development was delayed to the 10-month level. Persistently low ADC, suggesting ongoing ischaemia, was again demonstrated on MR scans at 16 (G) and 30 months. The patient underwent a hemispherectomy for intractable epilepsy at the age of 33 months and has remained seizure-free post-operatively. It is possible that

chronic exposure to mild overnight hypoxaemia had a deleterious effect on brain tissue compromised by chronic venous hypertension and ischaemia.

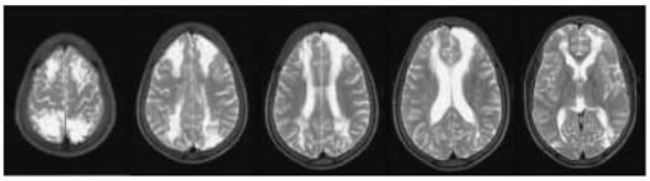

Figure 3.

This 8-year-old boy (Patient 1, Tables 2 and 3), one of twins, had uncomplicated sickle cell disease (SCD) but at the age of 6 years, had overnight pulse oximetry classified prospectively as normal (Kirkham *et al.*, 2001) although the mean was less than the 5th percentile for age (Urschitz *et al.*, 2003). His twin developed conditionally high internal carotid/middle cerebral artery velocities on transcranial Doppler (TCD) (maximum 192 cm/sec at the age of 8) but has not had a neurological event over follow-up of 13 years. This patient's TCD remained normal (maximum 144 cm/sec at the age of 8) but 2 months after this recording, he developed seizures and coma after surgery to drain a painful swelling of his left cheek, associated with fever, after a fall. Preoperative preparation had included hydration and blood transfusion to achieve a haemoglobin of 11.9 g/dl and haemoglobin S of 36% and blood pressure was above 110/50 mmHg (mean arterial blood pressure, MAP 70 mmHg) pre- and post-operatively even after the onset of coma. Intracranial pressure (ICP) was not measured. Initial T2-weighted MRI showed acute infarction with increased signal and swelling in both anterior arterial borderzones and the right posterior arterial borderzone, with mature infarction at follow-up as shown in the figure. TCD, Magnetic Resonance, including arteriography and venography, and four vessel cerebral angiography were normal. Motor function recovered completely. Psychometry showed significant cognitive impairment; compared to premorbid testing full scale IQ was reduced by 30 and performance IQ by 50 points (WISCIII). Covert infarction in the borderzones between the anterior and middle and posterior and middle cerebral arteries are common in SCD, probably because these areas are vulnerable to acute reductions in cerebral blood flow secondary to reduced cerebral perfusion pressure (CPP = MAP − ICP); this patient appears to have had an acute reduction in CPP despite maintenance of blood pressure, perhaps in relation to the cerebral oedema and undiagnosed raised ICP in a child with inadequate preconditioning for the insult experienced and normal cerebral vessels.

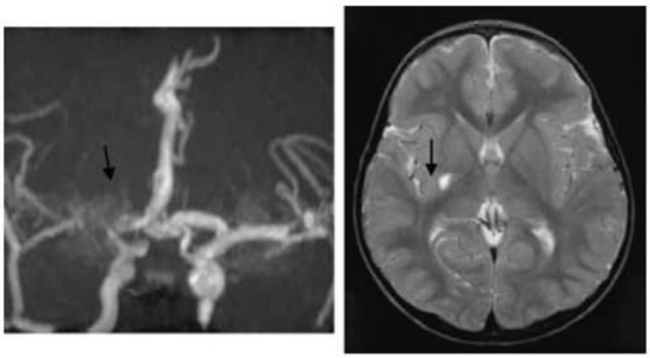

Figure 4.

Magnetic resonance angiogram (MRA) and imaging (MRI) from a girl (Patient 10, Tables 2 and 3) with sickle cell anaemia who had a sleep study showing dips and high transcranial velocities (up to 267 cm/second) for 8 years without symptoms but presented with a hemiparesis in the context of acute aplastic anaemia secondary to *Parvovirus*. Although the MRA shows severe turbulence with some 'moyamoya' collaterals (arrow), the MRI shows only a small infarct (arrow) and the patient made a complete recovery. This might be an example of the preconditioning effect of prior exposure to hypoxia in limiting the extent of tissue injury at the time of acute stroke but at the cost of irreversible vascular change.

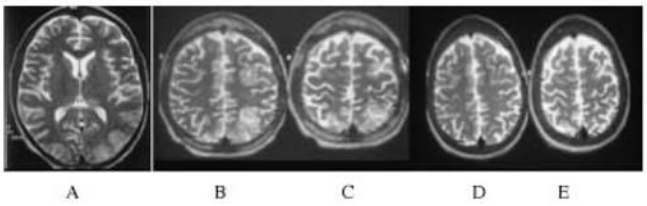

Figure 5.

This young woman with haemoglobin SS was born in Africa and immigrated to the United Kingdom aged 13 yrs where she remained well, with no painful or chest crises, until age 18 when she presented acutely with pain and dyspnoea. Blood pressure was 120/70 mmHg and oxyhaemoglobin saturation was 81% on admission. Haemoglobin was 3.8 with a white cell count of 66. Chest X-ray showed bilateral pulmonary infiltrates, reported as compatible with pulmonary oedema. Echocardiography showed moderate left atrial enlargement with left ventricular size at upper limit of normal; systolic function was good and tricuspid regurgitation trivial. She was confused with a Glasgow coma score (GCS) of 13/15 and appeared to have seizures with lip smacking and repetitive jerking of the right leg. When she regained full consciousness (GCS 15/15), she had a right hemianopia. Tone and power were normal in all limbs but reflexes were absent. TCD and MRA were normal. Axial T2 weighted MRI in the acute phase showed high signal changes in the left posterior occipital and bilateral high parietal regions (A, B, C) with hippocampal involvement (A). Repeat MRI 4 weeks later (D, E) showed resolution of all changes but the patient continued to have seizures with visual aura, staring, twitching of right hand, a sharp sensation on the right, hallucinations and memory loss. This is an example of reversible posterior leukencephalopathy (a poor term as there is obviously grey matter involvement and other regions are often affected) secondary to very acute and severe hypoxia in a patient with inadequate preconditioning and normal cerebral vessels. The involvement of the hippocampus in the acute process links this hypoxic insult to the subsequent intractable epilepsy.

Table 1

Key terms defined for the non-specialist

Apoptotic cell death – cell death programmed to occur over hours or days usually by chemical signals from its neighbours
Baroreceptor responses – response to input sensing pressure, usually in blood vessels such as the carotid sinus
Chemosensitivity – sensing of changes in respiratory gases (carbon dioxide and oxygen) in the brain stem and carotid bodies
Erythropoiesis – red blood cell production
Haemolysis – lysis of red blood cells with release of haemoglobin
Hypoxaemia – low blood oxygen
Hypoxia-Inducible Factor (HIF) – protein which is destroyed continuously when there is adequate oxygen but is stabilized during hypoxia and upregulates:
Erythropoietin – hormone which increases red cell production
Vascular endothelial growth factor (VEGF) – induces vessel growth (angiogenesis)
Endothelin – powerful constrictor of blood vessels
Nitric Oxide – powerful dilator of blood vessels
S-nitrosothiols (SNO) – molecules formed after the reaction of nitric oxide with a critical cysteine residue on proteins
Tidal volume – volume of air inhaled and exhaled at each breath

Table 2

Clinical, Transcranial Doppler (internal carotid (ICA)/middle cerebral artery (MCA), haematology, magnetic resonance angiography (MRA) and sleep study data from 19 patients from the East London cohort who had a central nervous system event during a prospective study (Kirkham *et al*., 2001)

Patient	Sex	Haemoglo binopathy	Age	Cerebro-vascular disease on MRA	Initial ICA/ MCA Velocity	Maximum ICA/ MCA Velocity during follow-up	Hb	Mean reticulocytes	Ts & As	Overnight oxyhaemoglobin saturation				Sleep study result
										Mean	Min	% <80%	% <90%	
1	M	SS	4.98	N	126	144	7.8	11.9	N	93.34	71	.96	11.6	Normal
2	M	SS	7.04	N	100	138	10.7	5.8	N	97.89	67	.28	2.18	Normal
3	M	SS	6.74	N	108	139	9.1	9.5	Y	98.23	86	.00	.35	Normal
4	F	SS	3.46	N	140	152	11.4	3.2	N	98.64	82	.00	1.03	Normal
5	M	SC	6.53	N	137	137	13.3	2.7	N	95.37	85	.00	1.29	Normal
6	M	SB	8.88	Y	137	137	12.6	13.5	N	95.77	85	.00	1.68	Normal
7	F	SS	9.63	Y	258	258	7.3	10.6	N	92.96	81	.00	13.5	Dips
8	F	SS	2.82	Y	143	144	10.9	11.5	N	97.70	90	.00	.13	Normal
9	M	SS	5.47	Y	116	141	6.9	17.1	N	90.21	76	.92	42.5	Normal
10	F	SS	9.43	Y	228	267	6.5	8.6	N	95.22	85	.00	1.32	Dips
11	F	SS	9.63	Y	134	134	8.1	11.6	N	95.68	41	.00	4.09	Normal
12	M	SS	4.74	Y	167	167	7.6	17.1	Y	90.58	75	.00	38.1	Dips
13	M	SS	4.69	Y	198	198	8.1	12.3	Y	87.00	76	.50	50.0	Mean <92%
14	M	SS	13.29	Y	131	131	8.1	18.4	N	87.26	77	1.05	97.5	Dips
15	F	SS	10.23	Y	72	88	6.8	–	N	91.93	81	.00	6.51	Mean <92%
16	F	SS	10.16	Y	109	124	11.1	16.9	Y	94.70	75	.29	3.37	Normal
17	F	SS	2.74	Y	125	125	8.5	8.5	N	97.05	84	.00	2.60	Normal
18	M	SS	11.01	Y	98	98	6.5	6.2	Y	85.00	75			Dips
19	M	SS	4.33	Y	134	134	10.2	16.3	N	92.41	89	.00	.00	Normal

MRA Magnetic resonance angiography, ICA internal carotid artery, MCA middle cerebral artery, Hb Haemoglobin, Dips desaturations, Ts & As Adenotonsillectomy.

Table 3

Clinical and neuroimaging data from the index and any recurrent central nervous system event in 19 patients from the East London cohort who had a central nervous system event during a prospective study (Table 2, Kirkham *et al.*, 2001a)

	First CNS event after screening (TCD and sleep study)				Second CNS event			
Patient	**Age**	**Context**	**Clinical**	**Type of event**	**Age**	**Context**	**Clinical**	**Neuroimaging**
1	8	Facial infection	R partial seizure prolonged, coma	Stroke	–			Bilateral borderzone infarcts (Figure 3)
2	9	Pain	Headache, dizziness, confusion	Stroke	12		Transient parathesia	Normal
3	11	Pain	Headache, diplopla, dizziness, VIth nerve palsy	TIA	12	Pain	Organic psychosis with hallucinations	Normal
4	9	Pain	Dizzy	TIA	.			Normal
5	0.1		Twitching right arm, blood stained CSF, ventricular haemorhage, hydrocephalus, ventriculoperitoneal shunt, seizures	TIA	9		Collapse, drooling, unable to see, unresponsive, seizures, incontinent, brain death	Venous sinus thrombosis, cerebral oedema (Sébire *et al.* 2005)
6	9	Severe OSA	Left hemiparesis	Stroke	11		R facial palsy	Atrophy left parietooccipital
7	10	Pain	Dizzy, headache, mild diplegia	Stroke	11		R hemiparesis	Increase in white matter abnormality
8	2	URTI	Floppy, unable to hold head, aphasic few hours, looked vacant, staggering to left	Stroke	7		R hemiparesis	New infarct middle cerebral artery territory
9	12	Pain	Severe headache, vomiting, neck stiffness, hypertension	Stroke	.			Haemorrhagic infarct
10	16	Aplastic	Dizzy, left paraesthesiae, left weakness, collapsed, shaking upper limbs, fluctuating conscious level	Stroke	.			New infarct basal ganglia (Figure 4)
11	15	Pain	Diplopia; divergent squint	TIA	.			‘Covert’ infarct, no change
12	3		Headaches, right sided weakness	TIA	6		Drags right foot	Increase in white matter abnormality
13	1.5		Not using right arm	TIA	6		R weakness, severe behaviour problems	‘Covert’ infarct, no change
14	15		Intermittent difficulty writing right hand	TIA	.			‘Covert’ infarct, no change
15	10		Squint	TIA	10		Intermittent blurred visison, 2*episodes of falling, unsteady afterwards, headache	Normal
16	10		Headache, blurring vision L eye	Seizure	13		Dizzy, not moving arm, headache, EEG-bursts slow both temporal R>L, discharges R posterior temporal	Normal
17	1.5	Diarrhoea, dehydration, femoral thrombosis	Extensor posturing, GCS 4	Seizure	3		Scratches table, wall or just blank, sleeps after	New ‘covert’ infarct
18	13	Pain	Headache, Unconscious, twitching arms, eyes deviated L, brief absences, visual disturbance	Seizure	13		Seizure lasting 7 minutes	New ‘covert’ infarct
19	4	Pain	Headache, uprolling eyes lasted few secs, flickering eyelids, afebrile. Talking to nurse-bizarre facial movements, uprolling eyes, twitching fingers, EEG normal	Seizure	4		Episodes shaking down right side*4 at night-wakes him	New ‘covert’ infarct

OSA, Obstructive sleep apnoea; TIA, Transient ischaemic attack; EEG, Electroencephalogram; R, Right; L, Left; GCS, Glasgow Coma Score.