

Case Report

Are we considering neonatal stroke early enough in our differential diagnosis?

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Abstract.

BACKGROUND: Neonatal stroke is an important cause of neurodisability in childhood and in later life. Delay in diagnosis is often inevitable due to the non-specific presentation, the lack of clinical signs, and not considering stroke early enough in the differential diagnosis.

CASE: We report the case of a baby who initially presented with apparent newborn “jitteriness” and abnormal movements. On the background of an unremarkable birth history and negative initial investigations, the baby subsequently developed focal seizures. The diagnosis was suspected to be neonatal stroke which was later confirmed on magnetic resonance imaging.

CONCLUSION: General Movements assessment is an established useful tool used in the assessment of such babies and proves helpful in evaluating whether movements are normal or pathological, in addition to prognosticating outcome. Cranial ultrasound is a commonly employed first-line investigation, however, initial normal intracranial appearances do not exclude stroke. Magnetic resonance imaging is the gold standard but may not be immediately available to all practitioners.

Keywords: Jittery, jitteriness, abnormal movement, seizure, neonatal stroke

1. Introduction

Stroke in the neonatal period can present with a wide range of varying, non-specific clinical manifestations such as lethargy, hypotonia, and apnea [1]. Given that these may be the presenting symptoms of a wide range of neonatal conditions, broad first line investigations are required to exclude other pathologies. Once these

have been excluded, or symptomatology indicates a neurological focus (abnormal movements; seizures; hemiparesis), stroke should feature more prominently in the differential diagnosis. Recognition and characterization of neonatal movements as normal, such as newborn “jitteriness”, or pathological, such as focal seizures, is key in determining the level of clinical concern and the timely initiation of investigations and treatment. This case report highlights the importance of assessing movements in those patients whose movements are suspected to be pathological and discusses the importance of initiating appropriate investigations promptly.

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2. Case history

A term female infant was reviewed on the postnatal ward on day 2 of life. The mother, who was in a non-consanguineous relationship, booked for antenatal care late in her pregnancy and was a gravida 2 para 0+1 (miscarriage at 10 weeks). She had an uncomplicated pregnancy with normal booking blood tests and antenatal ultrasound scans. There were no risk factors for sepsis and the baby was born in good condition by spontaneous vaginal delivery with APGAR scores of 9 and 10, at 1 and 5 minutes respectively. Vitamin K was administered via intramuscular injection.

The midwife caring for the baby had requested a medical review for witnessed right arm "jittery" movements which eased after a few minutes. This was also observed by the mother but reported by the father, as the mother spoke no English. Upon review, the baby handled well, with no features of dysmorphism and a normal neurological examination. A capillary blood gas revealed a normal blood glucose level and baseline blood tests including urea, electrolytes and bone profile were normal, excluding hypoglycemia and electrolyte imbalance as a potential cause. A cranial ultrasound scan was performed and was reported as normal by the

operator. The baby was kept on the postnatal ward with the mother.

The night shift midwife requested a further review of the baby as she was "not happy" with the movements that the baby was making and felt it was "not normal jitteriness". The father showed the reviewing doctor some episodes which he had recorded on his mobile telephone illustrating multiple rhythmic episodes of the right hand of 1-2 Hz, lasting for 30 seconds. A repeat blood glucose level was normal. The pediatric registrar was called to review, where upon multiple episodes of right hand and leg jerking were witnessed, each lasting 1-5 minutes. It was not possible to control the jerking movements by holding the limb. The episodes culminated in apparent opisthotonus and central cyanosis. The baby was immediately admitted to the neonatal unit.

Intravenous (IV) access was established: repeat blood glucose level and blood gas values were normal. Blood cultures were taken, IV antibiotics were started and the baby was kept *nil per oram*. Initial blood tests revealed a neutrophilic leucocytosis with a left shift, a C-reactive protein (CRP) at 6 mg/L, with normal urea, electrolytes, ammonia and clotting profile (neonatal reference ranges). Metabolic investigations

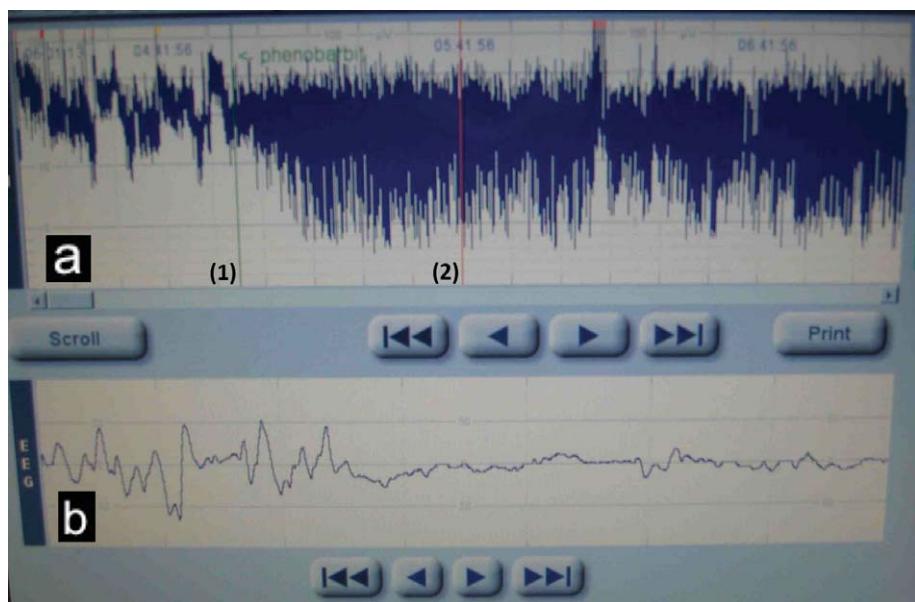


Fig. 1. Continuous amplitude-integrated electroencephalography (aEEG) tracing of the neonate on day 2 of life. Top trace (a): the initial trace demonstrates seizure activity as soon as monitoring is commenced. The labelled line (1) shows resolution of seizure activity with immediate effect after administration of a loading dose of phenobarbitone. Bottom trace (b): an expanded view of the brain activity at the labelled line (2) in the top trace post administration of phenobarbitone: normal brain activity is observed.

were also sent for plasma amino acids, in addition to urinary organic acids and reducing substances. A lumbar puncture was performed: clear and colorless fluid was obtained. No organism was seen on gram staining of cerebrospinal fluid (CSF) with normal glucose, protein and lactate levels. CSF was sent for herpes simplex virus (HSV) polymerase chain reaction analysis and IV acyclovir was commenced. Continuous amplitude-integrated electroencephalography (aEEG) was commenced revealing seizure activity: a loading dose of phenobarbitone was administered with immediate effect (Fig. 1).

Repeat cranial ultrasound was performed with reported normal appearances. After further clinical and electrical seizures overnight, she was commenced on maintenance phenobarbitone. Feeds were introduced after a 24 hour seizure-free period with normal serial neurological examinations and stable observations. Repeat CRP and full blood count were normal. Cranial ultrasound performed on day 4 revealed extensive left middle cerebral artery wedge shaped increased echogenicity (Fig. 2). The IV antibiotics were discon-

tinued on day 5 after the blood and CSF cultures were reported negative after 48 hours of incubation, suggesting that the cause of the seizures was unlikely to be related to infection. The IV acyclovir was discontinued after a negative HSV result. Repeat cranial ultrasound on day 5 demonstrated worsening left middle cerebral artery wedge shaped increased echogenicity (Fig. 3). A formal electroencephalogram was performed on day 7 revealing occasional spikes over the left parietal region of uncertain clinical significance. MRI performed on day 7 revealed loss of grey-white matter differentiation in the left frontoparietal area with effacement of the sulci and underlying white matter, in keeping with an acute left middle cerebral artery territory infarction (Fig. 4): this was confirmed on the apparent diffusion coefficient (ADC) imaging (Fig. 5). No space-occupying lesion was shown within the right hemisphere and posterior fossa structures appeared normal.

She was discharged home clinically well on full enteral feed by breast. A plan for outpatient echocardiography and consultant follow up 3 weeks post

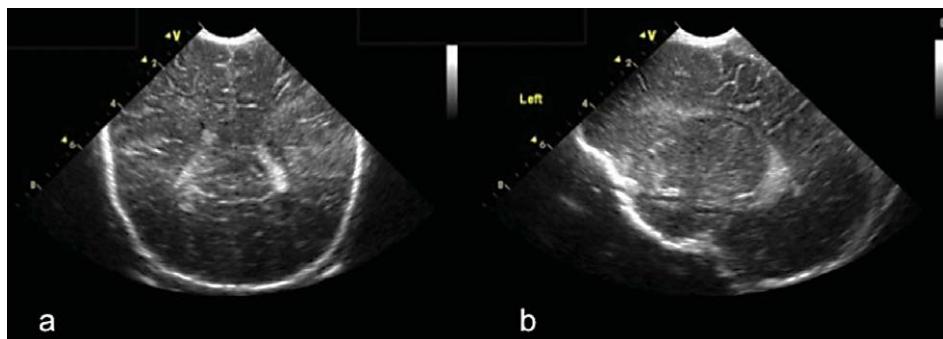


Fig. 2. Coronal (a) and left parasagittal (b) cranial ultrasound appearances of the neonate on day 4 of life. Extensive left middle cerebral artery wedge shaped increased echogenicity, best appreciated on the coronal view at the level of the choroid plexuses.



Fig. 3. Coronal cranial ultrasound appearances of the neonate on day 5 of life. Worsening left middle cerebral artery wedge shaped increased echogenicity is demonstrated on this coronal view at the level of the choroid plexuses.

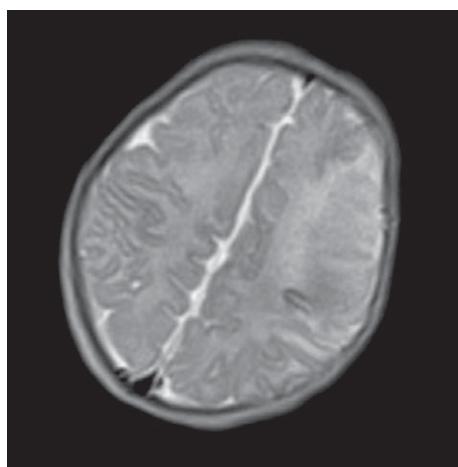


Fig. 4. A T2 weighted axial magnetic resonance image of the neonate on day 7 of life. There is high T2 signal with loss of grey-white matter differentiation in the left frontoparietal area with effacement of the sulci and underlying white matter, in keeping with an acute left middle cerebral artery territory infarction.

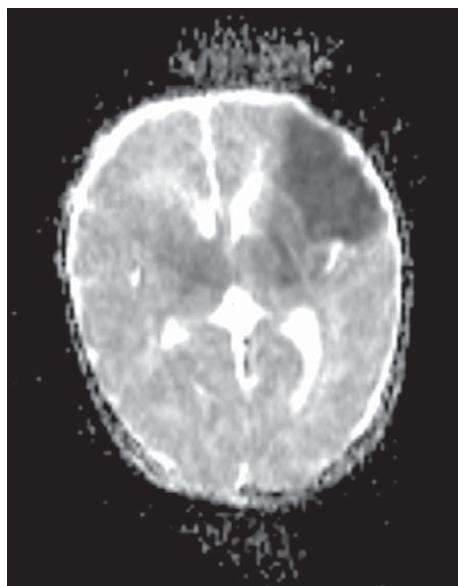


Fig. 5. An apparent diffusion coefficient (ADC) map from diffusion weighted imaging of the 7 day old neonate. Restricted diffusion is demonstrated in the left frontoparietal area (low signal on the ADC map image) in keeping with an acute left middle cerebral artery territory infarction.

discharge was established with further joint medical/physiotherapy clinic after 4 months. The results of the metabolic investigations and thrombophilia screen that were pending during her admission were negative, excluding these differentials as a cause for the insult.

3. Discussion

When assessing babies with a range of symptomologies, neonatal stroke is an important differential diagnosis to consider, particularly when commoner causes have been excluded. Neonatal stroke is defined as the disruption of blood flow to the brain within the first 28 days of life. There is overlap with perinatal stroke which is defined as occurring from week 28 of gestation to within the first 7 days of life [1, 2]. Neonatal stroke is reported to occur in approximately 1 in 4000 live births, with a likely higher incidence apportioned to 'clinically silent' strokes: cerebrovascular events that do not manifest with any clinically identifiable pathology [2]. Given the varied, sometimes non-specific, or 'silent' presentation, diagnosis is often difficult and subsequently delayed [3].

Neonatal strokes can be classified by: type (ischemic [80%] or hemorrhagic); the blood vessel affected (artery or vein); the timing of the injury (perinatal or neonatal, which can be difficult to ascertain given the overlapping definitions above); the timing of clinically apparent symptoms. Many infants are born following an uncomplicated pregnancy and delivery with no identifiable perinatal risk factors. Risk factors and potential causes can be categorized from mother to baby (Table 1).

Stroke accounts for approximately 10% of seizure presentations in the neonatal period, presenting with focal or multifocal (due to incomplete myelination of pathways) seizures [3]. If seizures are suspected,

Table 1
Risk factors for neonatal stroke (1, 2)

Location	Condition
Maternal	Autoimmune conditions
	Coagulation disorders
	Prenatal cocaine exposure
	Congenital heart disease
	Trauma, diabetes (prolonged second stage of labor, shoulder dystocia)
Placental	Thrombosis
	Abruption
Blood	Chorioamnionitis
	Polycythemia
	Factor V Leiden mutation
	Factor VIII deficiency
	Lipoprotein (a) deficiency
Baby	Disseminated intravascular coagulation
	Central nervous system infection
	Systemic infection
	Dehydration
	Extracorporeal membranous oxygenation (ECMO)

continuous amplitude-integrated electroencephalography (aEEG) should be employed as an initial measure. It has been shown that the onset of clinical or electrical seizures beyond 12 hours of birth, and clinically observed focal seizures, are predictive of stroke [4].

In our patient, a relatively common presentation of "jitteriness" was the initial concern of the practitioners and parents observing the baby. Further episodes were witnessed when it became clear that seizures, a focal neurological symptom, were developing. In contrast to the more common jitteriness which will usually cease by holding the limb, it was not possible to control our patient's jerking movements. It is possible that the general movements of the baby were abnormal prior to the witnessed initial clinical seizures; however, it is not a formal assessment that is routinely performed. A greater understanding of the differentiation and characterization of normal and abnormal movements may have prompted earlier recognition of such movements, allowing for initial investigations to be undertaken prior to the onset of focal seizures in our patient (Table 2).

The neonatal examination finding of jitteriness is common, with a quoted prevalence of up to 44% in a study of 936 newborns [5]. Jitteriness can be thought of as recurrent tremor [6], defined in the literature as an involuntary, rhythmical, oscillatory movement of equal amplitude around a fixed axis. Two types have been described: fine, with a high frequency (greater than 6 Hz) and low amplitude (lower than 3 cm); coarse, with a low frequency and higher amplitude [7]. Jitteriness or tremor can be benign or pathological. Benign jitteriness usually consists of fine tremor and is usually characterized by movements settling on soothing and suckling of the examiners finger [8]. These infants will usually appear well on examination and often will not have any perinatal complications. Multiple causes for neonatal "jitteriness" are well described. A non-exhaustive list includes: metabolic disturbances (glucose or electrolyte abnormalities); hormonal dysregulation (e.g. thyroid abnormalities); hypoxic ischemic encephalopathy; sepsis; drug withdrawal [9–11]. Suggested investigations for the presentation of jitteriness, as well as other symptoms, are again displayed in Table 2.

A more detailed description and exploration of infant movements has occurred since the publication of the General Movements (GM) assessment by Prechtl [12]. It has since been shown to become an attainable skill after only a few days of standardized training

Table 2

Suggested investigations for a range of potential neurological presentations. Investigations should always be considered in the context of the antenatal and perinatal history, and patient examination findings

Presentation	Suggested investigations
Simple jitteriness that settles on soothing or suckling	Blood glucose measurement if persistent
Persistent jitteriness, coarse jerking, significant perinatal risk factors	Blood glucose measurement Electrolyte measurement including ionized calcium Thyroid function tests Urine toxicology/drugs of abuse screen Partial/full septic screen Cranial ultrasound Magnetic resonance imaging Consider obstructive cause Blood glucose and electrolyte measurements (Na, Ca, pH) Partial/full septic screen Hemoglobin level Consider seizure as cause, see investigations below Consider cardiovascular/respiratory investigations Urine toxicology/drugs of abuse screen
Apnea	Blood glucose and electrolyte measurements Partial/full septic screen Hemoglobin level Consider seizure as cause, see investigations below Consider cardiovascular/respiratory investigations Urine toxicology/drugs of abuse screen
Excessive lethargy	Blood glucose and electrolyte measurements Partial/full septic screen Consider imaging if negative Blood glucose and electrolyte measurement
Seizures	Electroencephalography Septic screen including lumbar puncture and TORCH screen Urine toxicology Cranial ultrasound Magnetic resonance imaging Consider metabolic and genetics screen

[13], to correlate highly with the neurological outcome at all ages, and to have a sensitivity and specificity consistently superior to those of a traditional neurological examination [14]. Following this, there has been compelling evidence in the literature documenting its efficacy in predicting neurodevelopmental outcomes: a systematic review confirmed its effectiveness as a prognostic tool in predicting which infants will go on to develop subsequent neurodevelopmental disability [15].

General movements normally involve the entire body: they are complex, occur frequently, and for enough time to be observed. They manifest as variable

sequences of arm, leg, neck, and trunk movements, and wax and wane in intensity, force and speed, having a gradual beginning and end. Additionally, they are described as having rotations along the axis of the limbs with slight changes in the direction of movements creating the impression of complexity and variability [16]. It is useful for practitioners to have knowledge of normal neonatal movements, and by way of the GM assessment, it can be a useful tool in the evaluation of those infants about whose movements clinical concern has been raised.

We know that children who develop hemiplegia in infancy and childhood often have a period between birth and a year of age where there are no clinically apparent signs of the hemiplegia, reflecting evolving neuroplasticity after an early insult, such as neonatal stroke. It has been reiterated in the literature that the GM assessment is an accurate tool in predicting hemiplegia [17, 18].

The role of cranial ultrasound in confirming or refuting a range of possible diagnostic possibilities cannot be understated. However, performance and interpretation is limited by operator skill and knowledge. Initial (within the first 24 to 48 hours) normal intracranial appearances may be misleading: whilst the diagnosis of stroke cannot be fully excluded, subtle, non-specific appearances may evolve over serial scans, such as in the case of our patient. A high proportion of ultrasound scans reveal abnormalities strongly suggestive of infarction by around day 3 [19], and as such, serial scanning is advocated in those patients with suspected stroke. A caveat with this imaging modality is that occasionally, a small number of serial scans may be persistently normal, even with later diagnosed small middle cerebral or posterior cerebral artery territory infarcts on MRI [19].

Definitive MRI is required to confirm the diagnosis, preferably at an early stage in the diagnostic pathway to refine subsequent investigations and treatment. Precise description of the insult is mandatory in order to allow correlation with later potential cognitive and motor dysfunction or disability. Early MRI findings (location, depth and tract involvement) significantly contribute to predicting motor outcomes in those neonates with middle cerebral artery territory infarctions [20]. Additionally, quantified diffusion weighted MRI of the descending corticospinal tracts is also highly predictive of future motor outcome [21]. Computed tomography with angiography may be used but is not considered the best diagnostic option given the exposure to ionizing

radiation and the limitations in prognostication and delineation of anatomical structures.

MRI obtained earlier in our patient would have allowed us to consider that whilst sepsis could not be fully excluded at the time of initial presentation, it would be an unlikely cause of the stroke; particularly in the context of an unremarkable perinatal history, serial negative inflammatory markers and negative blood culture results at 24 and 48 hours. This would have allowed us to discontinue antibiotic and antiviral treatment at an earlier stage and further investigate other potential causes of the stroke. Second day seizures in the "well" baby in the absence of signs of infection, asphyxia, trauma and congenital anomalies, strongly raise the suspicion of stroke; exclusion of such pathology by obtaining an immediate MRI would have allowed us to optimize patient care.

It is worth remembering that MRI is only one part of the diagnostic pathway and should be used to help frame further decision making within the clinical context of the patient. Given that the GM assessment allows practitioners to differentiate between normal and abnormal movements, robust protocols and escalation to more experienced members of the pediatric team must be in place, not only to enhance trainee skill and knowledge, but to avoid unnecessary admissions for a full diagnostic work up in well babies. GM assessment also provides invaluable further information when MR is not immediately or readily available, which may be the case at some centers. Even when MRI is readily available, the assessment of general movements should be an important non-invasive and non-intrusive complementary assessment [22].

4. Conclusion

Neonatal stroke, whilst uncommon, is an important differential diagnosis to consider in neonates with witnessed abnormal movements on the background of an unremarkable medical history and normal initial investigations. In the case history above, we have illustrated that the description of "jitteriness" may be subjective, and should trigger consideration of a wider differential diagnosis, of which neonatal stroke is included. GM assessment is an important skill that can be acquired to inform practitioners practice and decision making regarding diagnostic, investigation and treatment pathways. Initial ultrasound imaging may be misleading given that appearances can evolve, advocating the need

for serial scanning until definitive MRI can be performed, as in the case of our patient. Early MRI scans are an important part of the prognostication process but may not be readily accessible or available to all practitioners: GM assessment is a proven useful tool to provide further information about potential long term neurodisability. Given the long term sequelae that can result from stroke, an early diagnosis is essential to identify the cause and to potentially initiate treatment and prevent recurrence.

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