**Accelerating the genetic diagnosis of neurological disorders presenting with episodic apnoea in infancy**

Bryony Silksmith1 MRCPCH, Pinki Munot2 MRCPCH, Luke Starling3 FRCPCH, Suresh Pujar1 MRCPCH, and Emma Matthews4 FRCP.

1Department of Neurology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

2Dubowitz Neuromuscular Centre, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

3Centre for Inherited Cardiovascular Diseases, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

4Atkinson-Morley Neuromuscular Centre, Department of Neurology, St George's University Hospitals NHS Foundation Trust, and Molecular and Clinical Sciences Research Institute, St George’s University of London, London, UK

Corresponding author: Emma Matthews

Atkinson-Morley Neuromuscular Centre, Department of Neurology, St George's University Hospitals NHS Foundation Trust, and Molecular and Clinical Sciences Research Institute, St George’s University of London, Cranmer Terrace, SW17 0RE, London, UK

Email: e.matthews@sgul.ac.uk

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**Summary**

Unexplained episodic apnoea in infants, including recurrent brief resolved unexplained events (BRUE) or events that are longer with abnormal history and/or examination can be a diagnostic challenge. Recurrent unexplained apnoea may herald a persistent, debilitating and potentially fatal disorder. Genetic diseases are prevalent among this group and particularly in those that present with paroxysmal or episodic neurological symptoms. These disorders are individually rare, challenging for a general paediatrician to recognise and there is often a delayed or even posthumous diagnosis (sometimes only made in retrospect when a second sibling becomes unwell). They can be debilitating if untreated but pharmacotherapies are available for the vast majority.

That any child should suffer from unnecessary morbidity or die from one of these disorders without a diagnosis or treatment having been offered is a tragedy and therefore there is an urgent need to simplify and expedite the diagnostic journey. We propose an "apnoea gene panel" for hospital specialists caring for any infant who experiences recurrent apnoea without an obvious cause. This may remove the need to pinpoint individual rare conditions, speed up diagnosis and improve access to therapy with the ultimate aim of reducing morbidity and mortality.

**Introduction**

Brief episodic apnoea, in otherwise generally well appearing infants, is a common but somewhat enigmatic paediatric presentation. The nomenclature of such events has changed over time but recently the term brief resolved unexplained events (BRUE) has been adopted. A BRUE is defined as an event occurring in an infant <1 year of age which is a sudden, brief (<1 minute), and now resolved episode of ≥1 of: cyanosis or pallor, absent, decreased, or irregular breathing, marked change in tone (hyper or hypotonia), altered level of responsiveness1. A BRUE is a diagnosis of exclusion and the term should not be applied if there is any clue in the medical history or physical examination to indicate an alternative (Panel 1). Classification of low and high risk BRUEs have been defined, with guidelines developed for the investigation and management of low-risk events but not for those that are high risk1. One of the criteria for high-risk BRUE is recurrence of events and this is more likely to herald a persistent, debilitating and potentially fatal underlying disorder. Apnoeic events lasting longer than 1 min, or occurring in association with abnormal history or examination or in children over the age of one lie outside the definition of a BRUE and are considered here as recurrent episodic apnoea (EA).

Genetic diseases are prevalent among infants with recurrent EA or high-risk BRUE, particularly those that present with additional paroxysmal neurological symptoms. These conditions share several features: 1.They are rare and a general paediatrician will not experience many. 2. Investigations may be normal unless performed during symptoms or abnormalities subtle and their relevance may only be appreciated when viewed by a specialist or in the context of multiple events. 3. Symptoms can be unusual and difficult for families to describe and phenotype can be variable. 4. Diagnosis is often delayed or even posthumous. 5. The majority can be treated symptomatically with available pharmacotherapies. 6. If untreated they can cause significant disability or death. 7. A genetic test is diagnostic.

Although there may be a window of relatively benign presentation with recurrent EA these genetic disorders can rapidly progress and may be fatal including sudden unexpected deaths. As most can be symptomatically treated, it is a tragedy that any child should die without a diagnosis, receive a posthumous one, or suffer with disabling symptoms due to diagnostic delay. Thus there is an urgent need to both simplify and expedite diagnosis.

Advances in genetic sequencing have led to large diagnostic gene panels being offered in the UK for many umbrella diagnoses e.g. epilepsy. This enables rapid diagnosis of any potential monogenic disorder presenting with a common symptom e.g. seizure without an obligate need to phenotypically pinpoint an individual condition or candidate gene, which can be time consuming, may not be possible early in the presentation and more than one monogenic disorder may have similar presentation. We propose a similar approach could be taken to design an “apnoea gene panel”.

In this viewpoint we review the presentation, investigation, and management of treatable monogenic paroxysmal neurological disorders that can present with recurrent EA in infancy. Our aim is to establish a list of disorders that could be considered as the basis for first line genetic investigations. We hope this may be advantageous in promoting early diagnosis and treatment of infants and young children presenting with unexplained recurrent apnoea early in their illness before a catastrophic deterioration occurs.

**Central Nervous System Disorders**

**Congenital Central Hypoventilation Syndrome (CCHS)**

Affected individuals with PHOX2B gene re-arrangements or mutations display a failure in autonomic control of breathing, lacking normal responses to both hypercapnia and hypoxia. Hypoventilation is most pronounced during non-REM sleep. CCHS typically presents in infancy with apnoea, BRUE or pulmonary hypertension due to chronic hypoxia. Children with CCHS will not display physical signs in response to hypoxia such as tachypnoea or increased work of breathing2. Autonomic dysfunction may affect other body systems. 15-20% of patients have associated Hirschprung’s disease known as Haddad syndrome3. Patients are also at risk of potentially-life threatening cardiac arrhythmias most notably sinus pauses sometimes necessitating pacemaker insertion4. Structural congenital heart disease is also more frequently seen5. Neural crest tumours are common and require surveillance. Temperature dysregulation, hypoglycaemia, hyperglycaemia and pupillary abnormalities are also reported2. Ventilator requirements vary; some patients only require support in sleep while others require 24-hour ventilation.

**Epileptic disorders**

Apnoea as the sole manifestation of seizures is well described in neonates. It is less commonly observed in isolation in older infants and usually accompanied by other seizure manifestations, but these can be subtle6. When taking the history, specifically asking for these subtle manifestations e.g. eye/head deviation, oromotor automatisms, stiffening/posturing or jerking of limbs, before, during or after the apnoeic episode is important.

While seizures due to any cause (structural, genetic, metabolic) may manifest with apnoea in infancy, we restrict the discussion to monogenic disorders here. Mutations in voltage-gated sodium and potassium channels are the most commonly reported monogenic disorders presenting as ictal apnoea in infancy. Our literature search identified mutations in SCN2A, SCN8A, KCNQ2, KCNT1, ATP1A3, BRAT1, FHF1, inherited GPI anchor deficiency-associated genes as well as some larger scale deletions (7q11.23, 1p36 and 18q). While mutations in PRRT2, KCNQ3 and SCN1A were not identified using apnoea as the search term, PRRT2 and KCNQ3 are recognised causes of benign familial neonatal-infantile seizures7, and SCN1A is a recognised risk factor for sudden death in infancy8. We therefore included these diagnoses in Table 1.

**SCN2A:** Pathogenic SCN2A variants are associated with a spectrum of epilepsies and neurodevelopmental disorders. Developmental and epileptic encephalopathies (DEE) account for the largest phenotype, typically presenting in the neonatal period with epilepsy, though 20-40% of cases may present after 3 months of age9. This distinction of 3 months is often helpful in predicting the type of mutation and therefore response to sodium channel blockers (SCBs). Infants <3 months may present with focal, tonic, tonic-clonic seizures or spasms; sometimes with features of Ohtahara syndrome or epilepsy of infancy with migrating focal seizures (EIMFS) +/- apnoea. They typically have de novo missense heterozygous variants with gain-of-function effect and have favourable response to SCBs such as phenytoin. DEE onset >3 months may present with features of West syndrome, Lennox-Gastaut syndrome, myoclonic atonic epilepsy, focal epilepsies or Dravet-like syndrome. They tend to have de novo loss-of-function variants and seizures are unresponsive, or worsened with SCBs, and are typically refractory to pharmacotherapy. Benign familial neonatal-infantile seizure is a milder phenotype of SCN2A, which resolves by 2 years and usually does not have long-term developmental sequelae. The­re is often a positive family history of neonatal seizures. Seizures are responsive to SCBs.

**SCN8A:** Phenotypic spectrum ranges from familial cases with benign infantile seizures (BFIS), normal cognition and usually normal interictal EEG, to early onset DEE, with severe cognitive impairment, pyramidal/extrapyramidal signs and cortical blindness10. Seizures associated with DEE are often prolonged focal with prominent hypomotor and vegetative symptoms (apnoea, brady/tachycardia, and cyanosis), that may evolve to unilateral and ultimately bilateral tonic and/or clonic seizures. One group reported generalised symmetric tonic seizures with autonomic signs as a clinical hallmark for SCN8A-DEE11. Epileptic spasms, myoclonus, and recurrent non-convulsive status epilepticus are frequently described. The seizures are typically pharmacoresistant in DEE, although SCBs, usually at supratherapeutic doses, are reported to have a beneficial effect in some patients with a gain of function (GoF) mutation. In contrast, BFIS are generally controlled on low-dose SCBs.

**KCNQ2:** Phenotype ranges from benign familial neonatal seizures to DEE. DEE typically presents in the neonatal period with tonic focal seizures, often associated with apnoea/desaturation, but may subsequently evolve into multiple seizure types12. The majority with DEE show burst-suppression pattern on interictal EEG, and there are some reports of a unique ictal EEG pattern consisting of initial lower amplitude fast activity, evolving into higher-amplitude theta-delta waves, which may aid early recognition and management13. SCBs are an effective treatment. The majority of treated patients achieve and remain seizure-free within the first year of life although DEEs tend to be pharmacoresistant14.

**KCNT1:** Most present in early infancy with migrating focal seizures or DEE15. Seizures are typically pharmacoresistant. Precision therapy with quinidine (due to its activity as KCNT1 channel blocker) showed limited success.

**BRAT1:** Rigidity and multifocal seizure syndrome, lethal neonatal (RMFSL) is caused by recessive pathogenic variants in BRAT1. Neonates present with microcephaly, hypertonia/rigidity, intractable focal seizures, apnoea and sometimes associated congenital heart disease16. Seizures may begin in utero or during the first week of life and may evolve into the pattern of focal seizures migrating between hemispheres. RMFSL is often associated with death in infancy or early childhood.

**FHF1:** Infants with FHF1-DEE usually present in first month of life with pharmacoresistant tonic seizures with autonomic features such as apnoea and bradycardia17.

**Inherited GPI anchor deficiency:** Transient recurrent apnoeas in the first week of life have been reported in infants with inherited GPI anchor deficiency, although whether they are ictal or not was not established with ictal EEG18. Kohashi et al. however reported an 11m old boy with PIGT mutation presenting with epileptic apnoeas, which responded to acetazolamide19.

**ATP1A3**

Mutations can result in numerous phenotypes including alternating hemiplegia of childhood, rapid-onset dystonia parkinsonism, and cerebellar ataxia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS)20. In those with alternating hemiplegia of childhood, presentation in infancy with apnoea (with or without epilepsy) is described. Aside from apnoeic seizure, apnoea most commonly occurs during bilateral plegic events with additional bradycardia, stridor, bronchospasm, hyperventilation, noisy breathing, and gasping for breath21. Symptoms can respond to flunarazine and/or anti-epileptics.

**GLUT1 deficiency syndrome**

Phenotype and age of onset of this neuro-metabolic disorder is highly variable. Infantile onset can be associated with multiple seizure types including myoclonic, absence and GTCS, paroxysmal movement disorder especially dystonia and ataxia with or without epilepsy, +/- intellectual disability22. The earliest clinical feature, often occurring between 0-3 months may be episodic apnoea and oculogyric movements23. Clinical features are due to impaired glucose transport across the blood brain barrier. Diagnosis is made by identifying a low CSF glucose level in the absence of hypoglycaemia and genetic confirmation of a mutation in the SLC2A1 gene. Ketogenic diet is the treatment of choice and can be extremely effective in controlling symptoms.

**Hyperekplexia**

Hyperekplexia is a rare movement disorder presenting in the neonatal period with generalised stiffness, excessive startle to stimuli and often tonic spasms. Consciousness is preserved during these events unless a secondary hypoxic seizure ensues24. In a 2013 study of 89 patients, apnoeas were reported in 56% of cases25. The identified causatives genes affect glycine neurotransmission, encoding the postsynaptic inhibitory glycine receptors or presynaptic glycine transporters found predominantly in the brain stem and spinal cord. The five recognised genes in order of frequency are GLRA1, SLC6A5, GLRB, GPHN and ARHGEF9, however 35% of patients will not have a mutation in a glycine-pathway gene26. Apnoea is most prevalent in infants with SLC6A5 and GLRB mutations, occurring in greater than 80% of cases25. Clonazepam is first line treatment with a high rate of symptom improvement reported. The Vigevano manoeuvre, flexing head and legs to the trunk, can be utilised to resolve an attack26.

**Neuromuscular disorders**

**Severe neonatal episodic laryngospasm**

Muscle channelopathies due to mutations in the SCN4A gene can present with episodic muscle weakness or myotonia. In an infantile phenotype termed SNEL: severe neonatal episodic laryngospasm27, recurrent apnoea due to myotonia of the laryngeal and respiratory muscles occurs with or without stridor. Associated stiffening or rigidity of the trunk and limbs due to generalised myotonia is common and these events are often erroneously diagnosed as seizures despite normal EEG. Other features can include cyanosis, bradycardia and loss of consciousness. Muscle hypertrophy and dysmorphic features may be prominent (Fig 1). The frequency of events is highly variable from a single isolated episode to twenty per day. Onset can be from birth up to 10 months. Recurrent apnoea can persist beyond the infantile period but tends to decrease and resolve within the first few years28. Triggers include inter-current illness, cold temperature or bathing and during feeds. Severity is variable29. Fatalities and posthumous diagnosis are reported27, 30. EMG demonstrates myotonia but can be technically difficult to perform and interpret. Symptoms are extremely responsive to sodium channel blockers.

**Paroxysmal extreme pain disorder**

This is due to mutation in the SCN9A gene causing a gain of function defect of the Nav1.7 sodium channel expressed in dorsal root ganglia and sympathetic ganglia sensory neurones. Symptoms of tonic posturing, harlequin skin flushing (see Fig 2), apnoea and syncope often begin in the neonatal period with extreme pain beginning later31, 32. Pain is commonly rectal, ocular or mandibular. Defaecation and eating are frequent triggers. As with many of the disorders we describe, epilepsy is often considered in the differential diagnosis but an ictal EEG excludes seizure. Symptoms are variably but often effectively improved with carbamazepine.

**Riboflavin transporter deficiency**

Previously known as Brown-Vialetto-Van-Laere syndrome, this is an autosomal recessive progressive disorder of cranial nerve motor neurons (VII, IX, X, XI, and XII) with facial weakness, dysphagia, tongue wasting and fasciculations, and sensorineural deafness33. Respiratory failure and/or ventilator dependence may be the presenting symptom at the age of 6–18 months in early-onset cases. Presentation with apnoea and breath-holding spells is also reported34. Brain stem auditory responses may be absent and is often a helpful diagnostic clue. Homozygous or compound heterozygous mutations in SLC52A2, SLC52A3, are reported33. Oral supplementation with high dose riboflavin helps to slow the progression and stabilisation of symptoms.

**Congenital Myasthenic Syndrome**

CMS often presents in infancy with ptosis, fatigable muscle weakness, respiratory and feeding difficulties. These disorders are caused by mutations in genes encoding proteins that have a major role in maintaining the structure and function of the neuromuscular junction. So far, 32 causative genes have been identified with CHRNE, RAPSN, DOK7, COLQ and CHAT being the most common35. Certain genotypes are well known to present with episodic apnoea and respiratory failure due to hypoventilation36. These most commonly include CHAT, RAPSN, and CHRNE (fast channel) but recurrent apnoea is also reported with SCN4A, CHRND, COLQ, COL13A1, SLC5A7, VAMP, MUNC13, MYO9A and SLC18A336, 37. Apnoea is often triggered by inter-current respiratory infections but can also be associated with fever, emotions and stress. Diagnosis is supported by the presence of a significant decrement on repetitive nerve stimulation or increased jitter on stimulation single fibre EMG. This test is not easy to perform or interpret however in an infant and not always available outside of a tertiary centre. The majority of the pre-synaptic forms of CMS respond well to treatment with acetylcholine-esterase inhibitors like pyridostigmine. 3,4-diamino-pyridine and salbutamol37. CMS caused by mutations in COLQ and DOK7 respond best to treatment with oral salbutamol37. In the majority, episodic apnoea resolves in childhood as demonstrated in the long term follow up data from McMacken’s cohort36.

**Metabolic and mitochondrial disorders**

We identified numerous references to a wide range of metabolic and mitochondrial disorders with apnoea including fatty acid oxidation disorders (short, medium and long chain acyl-CoA dehydrogenase deficiency), non-ketotic hyperglycinaemia, congenital hyperinsulinism and in-born errors of metabolism38-42. In the majority apnoea occurred within hours or days of birth and in association with rapid systemic compromise necessitating ICU admission. In others, there was a period of some weeks or months of apparent health which ended abruptly with a similar presentation or sudden death. It was quite rare that a “near miss” or resolved event(s) was reported before a catastrophic collapse occurred43-50. There were some notable exceptions however which we highlight in Table 2.

**Systemic disorders in which apnoea is a common symptom**

Our search terms identified a number of central nervous system and neuromuscular conditions in which apnoea was a common symptom but usually accompanying other systemic features.

**Central nervous system disorders**

Neurological syndromes included males with MECP2-related severe neonatal encephalopathy and females with MECP2 mutations causing Rett Syndrome, Joubert, Crisponi, Pitt-Hopkins, HIDEA (Hypotonia, Intellectual Disability and Eye Abnormalities), and PURA syndromes51-56. Infants with Crisponi Syndrome can present with extensive facial muscle contractions, from minimal stimuli or crying, hypertonia, opisthotonus, camptodactyly, and typical facial features. Muscle contractions attenuate during rest or when the infant calms down. These can sometimes present in the form of apnoeas53. We found multiple references to Prader Willi syndrome or other large scale deletions encompassing the Prader Willi region, Pompe’s disease and lysosomal storage disorders but these described apnoea in the context of sleep disordered breathing57-59.

**Neuromuscular Disorders**

**Congenital myotonic dystrophy**

Congenital myotonic dystrophy is a dominantly inherited disorder ofunstable CTG nucleotide repeat expansion in the DMPK gene. Babies present with a history of polyhydramnios and reduced foetal movements, hypotonia, weak cry, generalised weakness, feeding difficulties and apnoea or respiratory failure at birth60. The infants may have distinctive features, tented upper lip, ptosis, contractures and gastrointestinal motility problems.

**Congenital Myopathies and Muscular Dystrophies**

Congenital myopathies and muscular dystrophies are clinically and genetically heterogenous disorders that present at birth characterised by prenatal onset, hypotonia, arthrogryposis, variable pattern of muscle weakness (facial, ocular, axial, generalised, proximal or distal - depending on the genotype) and joint hypermobility or contractures. A significant proportion are associated with respiratory muscle weakness and may present with apnoea at or soon after birth, although these infants often present with respiratory failure rather than true episodic apnoea. Respiratory failure may be triggered during an intercurrent infection or aspiration. Congenital myopathies commonly presenting in infancy with respiratory insufficiency include those due to mutations in RYR1, MTM1 and nemaline myopathies61. The common dystrophies include merosin deficient muscular dystrophy (LAMA2, LMNA and Collagen 12)62.

**Spinal muscular atrophy**

Some inherited disorders affecting the peripheral nerves and motor neurons can present in infancy with respiratory symptoms including desaturations and apnoea. The most common is recessively inherited spinal muscular atrophy due to homozygous deletion of exon 5 of the SMN1 gene which leads to progressive loss of motor neurons in the spinal cord. Type 0 infants (onset at birth) may present with apnoea and ventilator dependence and Type 1 (onset <6months) may present with apnoea secondary to respiratory insufficiency in the first year during an intercurrent infection63. Three different drugs Zolgensma, Nusinersen and Risdiplam have recently been shown to ameliorate the progression of disease with the best response proportionate to earlier intervention64.

**Spinal muscular atrophy with respiratory distress type 1**

SMARD1 is an autosomal recessive disorder caused by mutations in the IGHMBP2 gene. Severity is variable but most present in the first 6 months of life with respiratory failure due to diaphragmatic weakness, weak cry, feeding difficulties and progressive distal lower limb wasting65. A proportion of patients have symptoms of autonomic dysfunction. Episodic apnoea from the age of 2 months is reported66 as is sudden death and post-mortem diagnosis. No effective therapy is available and outcomes are fatal in severely affected cases.

**CNTNAP1 associated congenital hypomyelinating neuropathy**

This neuropathy can also present with apnoea and respiratory insufficiency67. Nerve conduction velocity is severely reduced to <10m/s on neurophysiology studies, and nerve biopsy demonstrates severe abnormalities of the nodes of Ranvier and myelinated axons. No effective treatment is available.

**Approach to investigation of unexplained recurrent apnoea**

The myriad of potential causes when an infant presents with recurrent EA can make diagnostic workup challenging. We summarise a brief approach based on our literature search (Panel 1) and highlight pertinent investigations that may indicate a genetic diagnosis (Tables 1 and 2). Reviewing all investigations is beyond the scope of this review and we would direct the reader to other comprehensive references68. We focus on genetic neurological disorders but our literature search emphasised that cardiac causes are an important differential diagnosis mandating a detailed cardiac assessment in the evaluation or infants presenting with recurrent EA. Hitherto undiagnosed congenital heart disease, and cardiomyopathy, may be suggested by simple clinical examination, whilst these and less common defects such as anomalous coronary arteries, will be confirmed by electrocardiography (ECG) and echocardiography. On excluding structural anomalies, attention should turn to excluding arrhythmia. A normal resting ECG does not unequivocally exclude arrhythmia tendency. Where suspicion persists, a low threshold for ambulatory heart rhythm monitoring should be adopted. Co-inciding a typical clinical event with rhythm monitoring may effectively confirm or exclude an arrhythmogenic basis, whilst ectopy, non-sustained tachyarrhythmias and periods of AV block and pauses may be important warning shots. Longer periods of monitoring or an implantable loop recorder may also be enlightening, particularly when events are infrequent. Significant candidate genetic diagnoses include long QT syndrome (LQTS), where mutations in 3 genes (*KCNQ1*, *KCNH2*, and *SCN5A*) account for >75% of cases, Brugada syndrome or sodium channelopathy (*SCN5A*), or catecholaminergic polymorphic ventricular tachycardia (CPVT), most commonly as an autosomal dominantly-inherited *RYR2* mutation68-72. Diagnostic work up for epilepsy is required in suspected cases of ictal apnoea and also frequently for any infant presenting with recurrent EA without an obvious explanation. A normal interictal EEG does not exclude the possibility of the apnoea being seizure-related and a prolonged EEG capturing the ictal episode may be required.

There was a common theme among the genetic disorders that we highlight, that while an investigation may be diagnostic e.g. EEG, a normal result, especially if the test was not performed at the time of symptom occurrence, does not exclude the diagnosis. Access to an expert able to perform/interpret the test may also be limited and further delay the genetic diagnosis. Such tests do have important utility but speed can be of the essence in diagnosing these conditions and we would strongly advocate that genetic testing should not necessarily be excluded by a normal result or delayed for these specialist investigations.

In addition to involvement of a general paediatrician, infants with recurrent apnoea may need input from specialists for investigation e.g. cardiologists, ENT surgeons, gastroenterologists, pulmonologists, geneticists or neurologists. Although we focus on neurological causes of apnoea in this paper, as the presentation can be nebulous, it is important to raise awareness of any proposed gene panel widely among specialists.

**Proposed genetic testing**

We focussed on recurrent EA during infancy as the unifying symptom of all disorders reviewed in our literature search to generate an apnoea gene panel of treatable conditions that could simplify and accelerate diagnosis (Table 1 and 2). The ability and availability for genetic testing will vary between health care systems. In the UK we propose WGS (Whole Genome Sequencing) including trio analysis of proband and parents could be offered with analysis of a virtual gene panel that encompasses all conditions in Tables 1 and 2. This would mirror the approach that is available for many other umbrella diagnoses and allow the additional option of analysing the remaining genome in panel negative cases. While we have highlighted selected epilepsy and CMS genes it should be noted that any of these conditions could potentially present this way and we recommend existing complete epilepsy and CMS gene panels should be reviewed alongside clinical presentation if first line testing is negative. In other health care systems it may be more practical that selected genes which were most commonly reported to present with EA i.e. Table 1 is analysed. Notably some of the genetic disorders are due to gene or chromosomal re-arrangements or repeat disorders and must be analysed separately or micro-array performed.

Proposed criteria for genetic testing includes any child age 2 or under presenting to secondary paediatric care with more than one unexplained apnoea in whom common causes and structural cardiac, ENT, respiratory, brain malformation, infectious and gastro-oesophageal diagnoses have been excluded.

**Approach to management**

Specific treatment for each genetic disorder is outlined in Tables 1 and 2. Management requires a multi-disciplinary approach to support the child and family. This includes basic life support training for parents, non-invasive or bag and mask ventilation for emergency use are critical and can help in minimising morbidity and mortality73.

**Sudden death**

Unresponsive or apnoeic episodes may herald a risk of sudden death. The potential for these events to in turn reflect an inherited condition reiterates the importance of establishing a detailed family history and consideration of genetic screening. Even though a sudden death may be explained e.g. due to respiratory infection, the underlying genetic diagnosis may be missed with implications for families and future siblings. This is exemplified by congenital myasthenia where sudden death has been described in older siblings prior to the genetic diagnosis in a second child74. Epilepsy diagnoses included SCN1A and SCN1B although it is unclear whether the deaths are seizure-related or due to cardiac arrhythmias associated with these channelopathies8. Infants with hyperexplexia are at risk of sudden death both from central apnoea resultant of brain stem dysfunction and apnoea caused by tonic spasms24. Sudden deaths were also linked to CCHS and metabolic or mitochondrial disorders. Gene variants in the SCN4A gene associated with SNEL have been reported to be over-represented in a large SIDS cohort75.

**Future directions and challenges**

Introduction of any new genetic diagnostic approach will need regular evaluation and revision. We recognise our inclusion criteria remains broad and it would be beneficial to have improved data on whether there are other pointers to a high risk group that may benefit from prioritisation for more rapid gene sequencing and reporting. This could enable a more refined inclusion criteria.

We also note that new genes and phenotypes are constantly reported and the significance of gene variants with uncertain pathogenicity continuously reviewed which may impact upon the genes and disorders selected. It will be crucial to have the involvement of a geneticist to assist in gene selection and variant interpretation. Rapid reporting of results i.e. weeks not months, is desirable and feasible achievement of this may also influence type of testing offered e.g. WGS, gene panel etc.

Sudden deaths and posthumous diagnosis are linked to a number of the disorders in our proposed panel. Analysis of this panel could contribute to the investigation of sudden unexpected deaths and inform family planning for future siblings but this would require further research and evaluation.

**Conclusion**

Focussing on unexplained recurrent episodic apnoea presenting in infancy as an umbrella diagnosis, we have identified treatable genetic neurological disorders that we propose can form the basis of a diagnostic gene panel. Our aim is that this be used to simplify and accelerate diagnosis enabling early treatment that will prevent disability or in some cases death.

**Author contributions**

The PUBMED literature search was performed by BS. BS and EM proposed included articles based on review of published abstracts from this list. All authors reviewed and selected final references for inclusion and from their own files. All authors contributed to the generation of the tables. EM wrote the first draft of the complete manuscript, all authors drafted individual subsections and read and revised the completed manuscript.

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The paper has not been submitted to another journal, and has not been published in whole or in part elsewhere previously.

**Search strategy and selection criteria**

References were identified through a search of PUBMED. Inclusion criteria were studies of infants, young children or babies with the search terms apnoea or apnea, SIDS, cot death, sudden infant death, crib death, laryngospasm, apparent life threatening event or ALTE, brief resolved unexplained event or BRUE, long-term ventilation, failure wean from ventilator or failed ventilatory wean in whom a genetic disorder is identified. These latter terms take account of the fact that the same genetic disorders that cause EA can have multiple phenotypes or progressive presentations including unexplained ventilatory failure receiving long-term respiratory care. Any study type including poster abstracts available in English published from 1st Jan 2000 to 10th Dec 2021 were included. Studies detailing secondary causes of apnoea and apnoea of prematurity were excluded. Articles were also identified through searches of the authors’ own files and based on clinical experience. The final list, from 2702 considered references, was generated on the basis of originality and relevance to the broad scope of this review. If multiple references reported EA in the same condition a review article encompassing the spectrum may be referred to.

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**Figure Legends**

**Figure 1:** Facial dysmorphism and muscle hypetrophy in an infant with SNEL due to SCN4A mutation. A: Facial hypotonia, high forehead, low-set ears, short neck and high arched palate. B, C: Diffuse muscle hypertrophy

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**Figure 2:** Harlequin skin flushing characteristic of paroxysmal extreme pain disorder

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**Figure 3:** Summary of pertinent investigations and diagnostic considerations for an infant presenting with recurrent episodic apnoea

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| --- | --- |
| INFECTION | Chest X- ray, CSF, septic screen |
| REFLUX | GI work up including endoscopy |
| BRAIN MALFORMATIONS AND TRAUMA | MRI brain |
| EPILEPSY | EEG including prolonged EEG, MRI brain, CSF glucose |
| METABOLIC | Glucose, blood gas, lactate , ammonia, urine organic acids, plasma amino acids and plasma acylcarnitines, white cell beta-glucosidase activity |
| ENDOCRINE | Serum glucose, calcium, phosphate, magnesium |
| CARDIAC | ECG, echocardiogram, 24hr ECG, loop recorder |
| ENT | Airway and vocal cord assessment |
| SLEEP DISORDERED BREATHING | Sleep study |
| NEUROMUSCULAR | CK, EMG including NMJ studies |
| NEUROGENIC | Opthalmology, Brainstem auditory evoked response |

Panel 1: Summary of investigations

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| --- |
| **Key Messages** |
| * Recurrent unexplained episodic apnoea presenting in infancy can herald the onset of a progressive and debilitating genetic neurological disorder * The majority of these disorders can be treated with available pharmacological therapies * Diagnostic delay is common and compounded by their individual rarity * A simpler more rapid means of diagnosis is required to enable prompt treatment that can prevent morbidity and in some cases death * A diagnostic apnoea gene panel could achieve this by removing the need to pinpoint an individual disorder |