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Reflex sympathetic dystrophy: complex regional pain syndrome type I in children with mitochondrial disease and maternal inheritance

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ABSTRACT

Objective: Complex regional pain syndrome type I (CRPS-I), previously known as reflex sympathetic dystrophy (RSD), is an idiopathic condition characterised by localised, abnormally intense and prolonged pain, allodynia and autonomic nervous system changes (ie, swelling, skin colour and temperature changes and altered perspiration) that usually appear following a "noxious" trigger such as trauma or surgery. The objective of this report is to demonstrate that children with CRPS-I can have additional dysautonomic conditions secondary to an underlying maternally inherited mitochondrial disease, an association not previously published.

Methods: Medical records of about 500 patients seen by one paediatric metabolic geneticist were reviewed to identify children meeting established CRPS diagnostic criteria.

Results: CRPS-I was present in eight children in seven families, each of which also had additional functional/dysautonomic conditions, the most common (≥4 cases per condition) being gastrointestinal dysmotility, migraine, cyclic vomiting and chronic fatigue. All seven probands studied met Nijmegen (2002) diagnostic criteria for definite mitochondrial disease on the basis of the clinical signs and symptoms and biochemical analyses. Six of the seven families met our pedigree-based criteria for probable maternal inheritance.

Conclusion: In one tertiary-care paediatric genetics practice, children meeting the CRPS-I diagnostic criteria frequently had additional autonomic-related conditions secondary to maternally inherited mitochondrial disease, suggesting that mitochondrial DNA sequence variants can predispose children towards the development of CRPS-I and other dysautonomias. CRPS-I should be considered in patients with mitochondrial disease who complain of idiopathic pain. Maternally inherited mitochondrial disease may not be a rare cause of CRPS-I, especially in children who present with other manifestations of dysautonomia.

► Supplemental semi-structured interview is available online only at http://adc.bmj.com/content/vol93/issue5

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Complex regional pain syndrome type I (CRPS-I) is an uncommon "functional" pain condition characterised by localised, abnormally intense and prolonged pain, with abnormalities involving the sympathetic, somatosensory and somatomotor pathways.[1–4] The condition was previously known (and still generally referred to) as reflex sympathetic dystrophy (RSD), reflecting the prominent sympathetic involvement of the nerves innervating blood vessels and sweat glands of the affected area, often resulting in focal changes in skin colour, temperature, oedema and/or an altered sweat response.[3 5 6] Somatosensory involvement is also prominent, including pain and allodynia, the latter of which is defined by light touch or pressure being experienced as pain, which is generally severe.[1–4] Somatomotor involvement can include muscle weakness, as well as exaggerated tendon reflexes, tremor, dystonia and myoclonic jerks.[1] Trophic changes to the overlying skin can be present as long-term secondary effects. Unlike complex regional pain syndrome type II (previously known as causalgia), which by definition occurs following peripheral nerve injury, CRPS-I is defined in the absence of known nerve injury.[5] However, CRPS-I generally appears following a known "noxious" triggering event, including surgery, traumatic bone fractures, crush injuries and repetitive motion.[1 3 4 7] The aetiology and pathophysiological mechanisms of CRPS are not well understood.[1–4]

Treatment of patients with CRPS-I can be challenging, with substantial and prolonged disability occurring in many cases.[3 8] Treatment modalities include exercise, physical and occupational therapy, cognitive–behavioral therapy, systemic medications (especially anticonvulsants and tricyclic antidepressants), regional nerve blocks, spinal cord electrical stimulation and various surgical approaches including sympathectomy.[3] Although adults constitute the vast majority of reported cases, CRPS-I can occur in children and adolescents.[9 10] In paediatric patients, CRPS-I preferentially affects the lower extremities, and an excellent recovery is made in most cases, unlike adults where the opposites predominate.[9] In adult patients, about 20–35% are incapacitated for an extended period, and only 20–30% return to their former occupation.[8] The number of reported cases of CRPS-I has increased, particularly for those caused by work-related injuries of the upper extremities.[8]

In our clinical observation, CRPS-I can occur as one among many functional, neurological and/or endocrine conditions in children and adolescents with mitochondrial disease, an association not previously published. The term "mitochondrial disorder" encompasses hundreds to thousands of different genetic disorders in which pathology is based upon reduced ATP (energy) production by mitochondria. Although energy is a ubiquitous requirement for life, and thus mitochondrial disease can affect almost any cell type, in practice disease manifestations are predominately related to dysfunction of nerves and muscles, probably in part because of the high energy demands of these tissues.[11 12] It is generally believed that mitochondrial disease is fairly common, although perhaps rarely recognised, because of the extreme clinical variability among patients, intermittent and varying symptoms

within individual patients and the lack of sensitive, non-invasive diagnostic testing.

Some of the better-known mitochondrial disorders include MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, usually caused by the 3243A>G mtDNA point mutation), LHON (Leber hereditary optic neuropathy, usually caused by three different mtDNA point mutations) and Kearns–Sayre syndrome (usually caused by large mtDNA deletions). Prevalence estimates for these individual mitochondrial disorders range from 0.7 to 16 cases per 100 000,[13] but the vast majority of children with mitochondrial disease do not fit well within these or other named classifications, and the overall prevalence is at least one case in 8500.

It has also been our clinical experience that our patients with CRPS-I demonstrate "maternal inheritance." Mitochondrial disease may follow maternal, autosomal recessive or, rarely, other inheritance patterns. Maternal or "mitochondrial" inheritance occurs because mitochondria are cytoplasmic organelles that contain DNA (mtDNA), which is inherited directly from the mother (from the ova, the few sperm mitochondria that enter the ova do not replicate) without recombination.[11] It follows that all "matrilineal" relatives, defined as those individuals related entirely through women, should share the same mtDNA genomic sequence in the absence of a recent mutation. However, because of the ubiquitous nature of energy metabolism and many unique features of mitochondrial genetics, individuals with mtDNA mutations demonstrate considerable intra- and interfamilial clinical heterogeneity in terms of severity, age of onset and clinical symptomatology.[11 12]

In this case series, eight children from seven families diagnosed with CRPS-I who met criteria for mitochondrial disease, of which six of the seven families also met criteria for maternal inheritance, are discussed. It is important to identify these cases as there are practical implications regarding co-morbid conditions and treatment.

METHODS

Subjects

A retrospective chart review was performed on approximately 500 children evaluated by the senior author (RGB) over a three-year period in the outpatient Genetics Clinic at Childrens Hospital Los Angeles (CHLA) to identify medical conditions or treatments consistent with dysautonomia or chronic idiopathic pain. For each potential match, a comprehensive chart review was performed on the patient and any known siblings that had been evaluated as patients. Patients that met the International Association for the Study of Pain (IASP) diagnostic criteria for CRPS-I defined in 1994[4] (see box 1) were "recruited" for the present case series. Our methods were designed to identify all patients that meet IASP criteria for CRPS-I, without regard to any clinical parameters such as the presence of additional clinical manifestations, inheritance pattern, laboratory data or other diagnoses (eg, mitochondrial disease). Using this procedure, six living children meeting CRPS-I criteria were identified, including one sibling pair. An additional two children who met the criteria for CRPS-I, but who had died before the interval of the chart review, were included. Twelve "control" families were retrospectively and anonymously ascertained from the same outpatient genetics clinic through a child with either an established autosomal recessive (five cases) or a non-inherited condition (chromosomal aneuploidy, six cases or vascular malformation, one case). The CHLA Institutional Review Board approved all activities associated with this study.

Mitochondrial disease "Nijmegen" criteria

There is no "gold standard" for diagnosis of mitochondrial disease, although two systems, often referred to as the Melbourne and Nijmegen criteria, are in common use. On the basis of retrospective chart reviews, the Nijmegen mitochondrial disease diagnostic criteria in infants and children[14] were applied, because the Melbourne criteria require a muscle biopsy, which was not performed in all of our subjects owing to concerns associated with invasiveness and costs. The Nijmegen diagnostic criteria uses a numerical scale (range 0 to 12) for the number of clinical (muscular, CNS and selected other systems), metabolic, histopathologic and radiological findings present. This scale is used to classify the likelihood of a respiratory chain disorder in patients as "unlikely" (score 0–2), "possible" (score 3–4), "probable" (score 5–7) or "definite" (score 8–12). As our chart review did not find results relating to many of the items, especially histopathological and magnetic resonance data in many patients, the scores obtained were an underestimate.

Pedigree analysis

Although the Nijmegen criteria are useful for clinically assessing the presence of mitochondrial disease in a single patient, they do not consider the inheritance pattern of the condition.[14] To investigate the inheritance pattern, a quantitative methodology was applied to pedigrees previously drawn as part of routine clinical care in the seven CRPS-I and 12 control families. The procedures for pedigree production are standardised in our genetics clinic and follow a semi-structured interview format that allows for consistency across all interviewers and families (see supplementary data). In particular, the interview places an emphasis on functional disorders, especially migraine, muscle pain, gastrointestinal dysmotility, depression and chronic fatigue, as these and related conditions (fig 1) are especially common among the identified patients and affected relatives in families with maternally inherited mitochondrial disease.[15]

The number of neuroendocrine conditions recorded in all matrilineal first- and second-degree relatives of the identified patient was added and divided by the number of relatives to give the "number of neuroendocrine conditions per matrilineal relative". Similarly, the number of neuroendocrine conditions present per non-matrilineal relative was calculated. The quotient of the two resulting numbers is the "maternal inheritance ratio". Pedigrees were labelled as "probable maternal inheritance" if neuroendocrine conditions were reported at a prevalence of at least one condition per matrilineal individual, and the maternal inheritance ratio was at least 3 (meaning that neuroendocrine conditions are at least three-fold more common in the maternal versus the paternal relatives). On the opposite end, families were labelled as "probable non-maternal inheritance" if there were less than 0.5 neuroendocrine conditions per first- and second-degree matrilineal relative or the maternal inheritance ratio was less than 2. Families scoring between these two designations were labelled as "indeterminate". Figure 1 illustrates how the calculations are made and interpreted. Further discussion of the method can be found in the supplementary data.

Laboratory analyses

Diagnostic testing of the children was performed by various laboratories to support the diagnosis of a mitochondrial disorder and to evaluate other possible diagnoses. The results were interpreted using normative data provided by the respective laboratories. Quantification of urine organic acids by gas

Box 1 Complex regional pain syndrome (CRPS-I) diagnostic criteria

(1) The presence of an initiating noxious event or a cause of immobilisation.
(2) Continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event.
(3) Evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of pain.
(4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Modified research diagnostic criteria for complex regional pain syndrome proposed by Bruehl *et al* 1999[2]

(1) Continuing pain that is disproportionate to any inciting event.
(2) Must report at least one symptom in each of the four following categories:
(a) Sensory: reports of hyperesthesia.
(b) Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
(c) Sudomotor/oedema: reports of oedema and/or sweating changes and/or asymmetry.
(d) Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
(3) Must display at least one sign in two or more of the following categories:
(a) Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch).
(b) Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry.
(c) Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry.
(d) Motor/tropic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

chromatography/mass spectroscopy was performed in each identified patient to detect elevations of lipid and carbohydrate metabolism consistent with mitochondrial dysfunction. In selected cases, enzymatic activities were performed on skeletal muscle obtained by biopsy in order to determine the site of the block in the respiratory chain, and hence also to provide strong evidence for the presence of mitochondrial disease. Molecular analyses were performed as part of an earlier published study in which approximately 90% of the mtDNA was screened for the presence of heteroplasmy, the co-existence of two different mtDNA species (eg, mutant and normal), using temporal temperature gradient gel electrophoresis (TTGE).[16] Many mtDNA mutations are found in the heteroplasmic form (discussed further in supplementary data).

RESULTS

Eight children among the about 500 reviewed fulfilled the IASP criteria for CRPS-I (box 1). In each case, the child was disabled by pain and weakness during the episodes, with a full recovery regarding all CRPS-I-related manifestations following the episodes. Six of the children have had at least one "severe episode" meeting the very strict proposed modified CRPS-I diagnostic criteria (box 1).[2] Severe episodes generally lasted for a few weeks, although the duration ranged from a few days to as long as several months. Table 1 lists the signs and symptoms of CRPS-I in each of the children.

In addition to the relatively infrequent "severe" episodes in these six children, all eight children had frequent "mild" episodes. These episodes were usually limited to localised pain but sometimes were accompanied with dysautonomic features and often did not satisfy the IASP criteria for CRPS-I.[4] Symptoms generally occurred in the lower extremities triggered by exercise, viral illness, fasting or fatigue, although symptoms in the hands (often triggered by excessive writing) and other body surfaces did occur. These mild episodes, sometimes referred to by the families as "muscle cramps", were also frequent among the matrilineal relatives (including six of the nine siblings that were queried) as indicated by their history and examination. Manifestations of CRPS-I, both severe and mild, were always localised and almost always asymmetrical. Anecdotal information regarding response to treatment is listed in table 2.

The following case reports were selected to assist clinicians, in particular to illustrate how CRPS-I can exist in apparently "normal" children who would not necessarily be considered as candidates for having "mitochondrial disease".

Case A

This Caucasian/Hispanic girl's elder sister (fig 1, bottom) was followed at our institution since early infancy with apnoea, gastroesophageal reflux disease (GERD), absence seizures, migraine, cyclic vomiting (resolved with amitriptyline (Elavil)), depression and other conditions. Her elder brother (case 1 in tables 1, 2 and supplementary table 1) suffered from CRPS-I following the resection of a lipoma on the upper back, as well as multiple "dysautonomic" episodes (loss-of-consciousness with autonomic signs and a normal EEG), chronic fatigue and clinical depression (successfully treated with citalopram in both siblings (Celexa)). The younger sister (case 2 in tables 1, 2 and supplementary S2) was in normal health except for GERD in infancy, migraine headaches, urinary frequency and partial elective mutism, when at age 9 years she suffered a traumatic open fracture of the left radius and ulna. Starting 2 days later, severe pain, allodynia and weakness in the entire extremity resulted. Examination revealed swelling, a darkened colouration, decreased temperature and muscle weakness. Signs and symptoms were well demarcated in a glove-like distribution. Severe symptoms lasted for several months and appeared to improve with amitriptyline and with physical therapy. Occasional symptoms confined to that extremity still occur 3 years later. Migraine headaches and generalised muscle cramps respond in a highly dose-dependent manner (requiring 1 to 1.2 mg/kg/day) to amitriptyline.

Case B

A Caucasian/Filipina female (case 7 in tables 1, 2 and supplementary table 2; fig 1, top left) had a past medical history remarkable only for infantile failure-to-thrive, episodic hypothermia (lowest 33.5°C) and joint pain, until at age 14 years she fell during gymnastics and this was associated with right foot numbness. Over the next 5 days the foot became cold and swollen with colour alternating between pallor and cyanosis in a stocking-like distribution. In addition, she suffered from parasthesias, loss of pain, touch and pressure sensation and the inability to walk. Physical examination confirmed the patient's history and included severe right lower extremity muscle weakness. Doppler examination was unremarkable. All

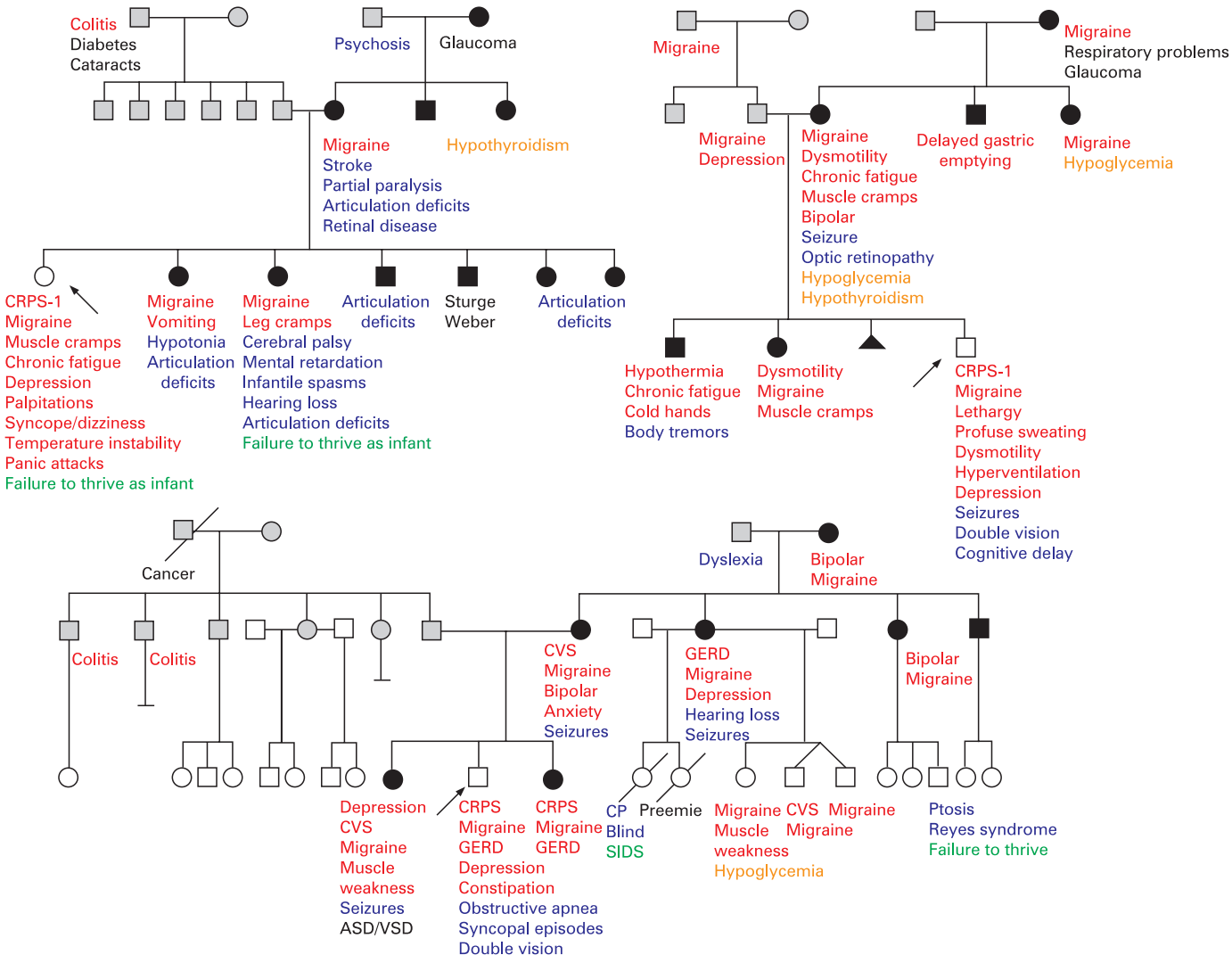

Figure 1 Pedigrees of three of our families. Pedigrees of cases 7 (upper left), 3 (upper right) and 1 and 2 (lower) are shown. Black and grey symbols denote first- and second-degree matrilineal (same mtDNA sequence as the proband) and non-matrilineal relatives, respectively. Only conditions in those relatives are scored in this method. Arrows denote probands with CRPS-I (case 1 in the lower pedigree; case 2 is his younger sister to the right of the arrow). Conditions counted in our quantitative pedigree analysis method are labelled in colour (red, functional; blue, other neurological; orange, endocrine; green, constitutional, see supplemental data for details); conditions not counted yellow are labelled in black (non-endocrine). In the lower pedigree, 22 neuroendocrine conditions in seven first- and second-degree matrilineal relatives averages 3.1 conditions per matrilineal relative. In the corresponding non-matrilineal relatives, three neuroendocrine conditions in nine relatives average 0.33 conditions per non-matrilineal relatives. The maternal inheritance ratio is thus 3.1/0.3 = 9.4.

manifestations resolved on the fifth day, yet briefly returned in the same extremity twice more in the following few months associated with psychological stress. In the past 10 years she has developed additional episodic phenomenon including migraine characterised by headache and sensory distortion (visual, gustatory, tactile and proprioceptive), stress-related anaesthesia in both upper and the lower right extremities, pain in her neck and four extremities, and palpitations not associated with anxiety. She once lost the use of her dominant hand for 4 days followed by pain for two additional weeks after excessive writing during final examinations. She is treated with Sertraline HCl (Zoloft) for depression. At age 18, physical examination was remarkable only for decreased touch sensation and profound transient muscle weakness (0/5 ankle dorsiflexion) in her left leg. Migraine-like and extremity findings resolved on treatment with amitriptyline (20 mg at night). She is highly intelligent, completed college and worked as a White House intern.

The reason for referral to the genetics clinic and the degree of total-disease-related disability ranged greatly among our cases. Five of the eight children were referred to the genetics clinic for non-CRPS episodic, autonomic-related clinical manifestations (table 2), before the onset of substantial CRPS-I-related manifestations. The remaining three patients (subjects 3, 4 and 7 in table 2) were referred initially to the genetics clinic for CRPS-I manifestations. In addition to dysautonomia, all eight children suffered from other neurological and non-neurological disorders (table 2). Four children had mental retardation and other severe neurological disease manifestations; two of whom died of their disease. Four cases attend/attended regular schools, although days missed from school are frequent owing to multiple autonomic-related symptoms.

All seven children (excluding the younger sister of our affected sibling pair, whom was not so tested) had abnormal quantitative urine organic acid profiles consistent with

Table 1 CRPS-I-related clinical manifestations in our subjects

Case	Age of onset of CRPS-I	No of CRPS-I episodes	Triggering event (for severe episodes if subject has severe and mild types)	CRPS-I-related episodic clinical manifestations
1 *I, M*	9 years	Two severe; multiple mild	Surgical excision of a lipoma on the upper back	Severe pain, swelling and erythema following both of two lipoma resections. Also, exercise can trigger leg pain, swelling and anaesthesia in the legs
2 *I, M*	9 years	One severe; multiple mild	Traumatic radial fracture	Severe pain, swelling and colour change to entire upper extremity following the fracture
3 *I*	Birth	Multiple mild	Many, including diet and viral infections	Pain, pallor and swelling to feet, profuse sweating
4 *I, M*	4 years	14 severe; multiple mild	Viral infections, influenza vaccine and no known trigger	Severe pain, allodynia, anaesthesia, parasthesia, erythema, weakness and inability to bear weight
5 *I, M*	19 months	One severe; multiple mild	Central line placement in groin and no known trigger	Pain, swelling, and change in colour and temperature to one leg following central line placement. At other times, an extremity has been tender, pallor and cold to touch. Frequent muscle cramps in the wrists without other findings
6 *I, M*	4 months	Multiple severe and mild	Sun exposure, minor trauma including phlebotomy and a blood pressure cuff	Migratory tenderness, swelling and change in skin colour and temperature to the extremities, blotchy red elliptical indurated skin lesions with overlying erythema (biopsy of a skin lesion revealed inflammatory cells and necrosis)
7 *I, M*	14 years	One severe; several mild	Fall during gymnastics	Right foot numb, alternating pallor and cyanosis in stocking-like distribution, parasthesias, loss of touch and pressure sensation, and inability to walk secondary to severe weakness and allodynia, idiopathic swelling and tenderness to breasts
8 *I*	6 years	Multiple mild	Sun exposure, fatigue	Arm and leg cramps, colour change (cyanosis, pallor or blotching rash), muscle weakness and disability

I, case meets the International Association for the Study of Pain (IASP) diagnostic criteria for complex regional pain syndrome. *M*, case meets the modified research diagnostic criteria for complex regional pain syndrome proposed by Bruehl *et al* 1999.[2]
Nerve condition velocities and electromyogram were normal in our patient with the most severe CRPS-I (case 4) a month after the recovery of the ability to walk when clinical symptoms were at a minimum.

Table 2 Non-CRPS-I-related clinical manifestations in our subjects

Case, NJM* score	Non-CRPS-I, episodic autonomic-related or "functional" clinical manifestations	Other neuromuscular-related clinical manifestations	Other clinical manifestations	Treatment
1 8 points	Syncopal episodes that mimic seizures, migraine, GERD, chronic constipation, sleep apnea	Mild rhabdomyolysis, exercise intolerance, double vision	Fasting-related symptoms, exacerbation of symptoms with minor illness, family history of SIDS	CRPS-I responded to physical therapy, most episodic symptoms improved with amitriptyline
2 6 points	Migraine, frequent urination, GERD, chronic constipation	Exercise intolerance, muscle weakness	Elevated transaminases, exacerbation of symptoms with minor illness	CRPS-I responded to physical therapy, migraines responded to amitriptyline
3 12 points	Cyclic vomiting as an infant, migraine, gastrointestinal dysmotility, pseudo-obstruction, hyperventilation, chronic fatigue, hiccups, sleep problems	Mild developmental delay, double vision, loss of developmental milestones, delusions, paranoia, mixed seizure disorder, hypotonia	Short stature, fasting-related symptoms, exacerbation of symptoms with minor illness	CRPS-I responded to dietary changes, amitriptyline not tolerated owing to lethargy
4 9 points	Chronic nausea, abdominal pain	Rhabdomyolysis (not at time of CRPS-I), staring spells, seizures, exercise intolerance, abnormal myelination, muscle weakness	Exacerbation of symptoms with minor illness, elevated transaminases	CRPS-I symptoms responded to amitriptyline
5 8 points	Cyclic vomiting syndrome, chronic diarrhoea, temperature instability, migraine, frequent urination, chronic fatigue, apnoea episodes as infant, sleep problems	Mild developmental delay, ataxia, hypotonia as infant	Exacerbation of symptoms with minor illness, family history of SIDS	CRPS-I and cyclic vomiting manifestations all resolved on caffeine and amitriptyline
6 10 points	Severe gastrointestinal dysmotility, cyanotic episodes, unexplained hyperthermia, abdominal pain (inferred from crying and tenderness), three episodes of cyclic vomiting	Severe developmental delay, hypotonia, strabismus, pigmentary retinopathy, staring spells, microcephaly	Growth retardation, failure-to-thrive, exacerbation of symptoms with minor illness, small atrial septal defect, pancytopenia, died from pneumocystis	CRPS-I responded to propranolol
7 10 points	Hypothermia (to 33.5°C), migraine, muscle pain, palpitations (without anxiety), syncope, dizziness, chronic fatigue, panic attacks, depression	Exercise intolerance, muscle weakness	Failure-to-thrive as an infant, exacerbation of symptoms with minor illness	Head, neck and limb pain responded to amitriptyline, depression responded to venlafaxine
8 12 points	Cyclic vomiting syndrome, GERD, chronic fatigue,	Developmental delay, mild spastic quadriplegia, seizures, choreoathletoid movements, exercise intolerance, left-sided facial weakness, hypotonia, myotonic facies, decreased white matter, stroke-like episodes	Growth retardation, renal tubular acidosis, patient died at 6 years of age	CRPS-I responded to caffeine, cyclic vomiting and extremity pain responded to amitriptyline

*NJM, Nijmegen diagnostic criteria for mitochondrial disorders in infants and children. Scores of 8–12 points = "definite", and 5–7 points = "probable" defect of the respiratory chain.

mitochondrial dysfunction, most notably elevated ketones, Krebs cycle intermediates and dicarboxylic acids, in specimens obtained early in autonomic-related episodes (CRPS-I, cyclic vomiting, etc) (see supplementary data). Profiles were typically normal when asymptomatic or after dextrose-containing intravenous fluids were administered. Abnormal results were found on muscle respiratory chain enzymology in two out of four cases (see supplementary table 2). Mitochondrial DNA heteroplasmy[16] was identified in three out of six cases tested (see supplementary data).

On the basis of the above information, all eight children were given a clinical diagnosis of mitochondrial disease before initiation of this retrospective study. In support of this diagnosis, all seven of the index patients were found to meet the Nijmegen diagnostic criteria for mitochondrial disorders in children at the highest level: a "definite disorder of the respiratory chain" (table 2).[14] The younger sister of case 1 only met Nijmegen criteria for a "probable disorder of the respiratory chain", mostly because of a relative absence of diagnostic testing, as such testing had been performed in her brother (subject 1) and elder sister (fig 1, bottom), who were both found to meet the "definite" Nijmegen criteria. In some cases, the children met the respective Nijmegen diagnostic labels on the basis of clinical and body fluid metabolite data alone, despite the absence of more specific enzymological and histological studies.

The pedigrees in six of the seven families met criteria for "probable maternal inheritance" by both our previously published guidelines[17] and by our novel quantitative pedigree-analysis-based criteria (fig 2). Three of these six pedigrees are illustrated in figure 1. The remaining CRPS-I family demonstrated an indeterminate result by both our past and present modalities. All of our 12 control families met both our previous and our present quantitative pedigree-analysis-based criteria for "probable non-maternal inheritance" (fig 2). CPRS-I and control families had a mean number of conditions per matrilineal relative of 1.9 and 0.18, respectively ($p = 0.003$), and a mean maternal inheritance ratio of 6.7 and 1.3, respectively ($p = 0.003$).

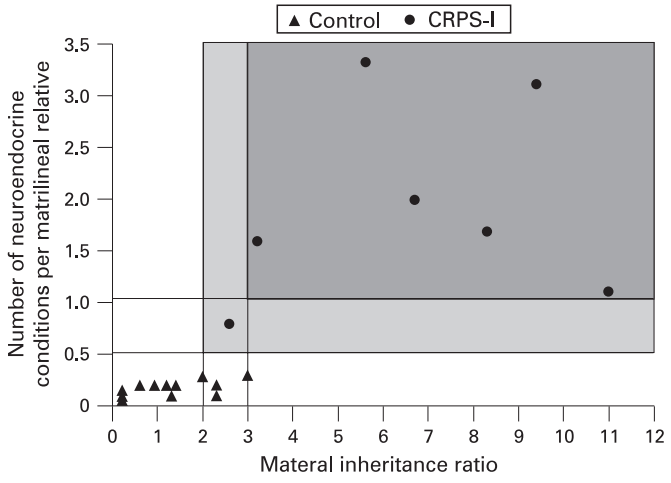

Figure 2 Labeling of pedigrees as "probable maternal inheritance" , "probable non-maternal inheritance" or "indeterminate." The CRPS-I and control families are represented by circles and triangles, respectively. The heavily shaded, lightly shaded and unshaded areas correspond to our criteria for labelling families as "probable maternal inheritance", "indeterminate" and "probable non-maternal inheritance," respectively. The maternal inheritance ratio is defined in the text and in figure 1. This figure demonstrates that our CRPS-I and control families are distinctly different in terms of both the absolute (x axis) and relative (y axis) number of neuroendocrine conditions reported per matrilineal family member.

DISCUSSION

All eight patients meeting CRPS-I criteria in one tertiary-care paediatric genetics practice were given a clinical diagnosis of a mitochondrial disorder, and this diagnosis was supported in each by the retrospective application of the Nijmegen criteria for mitochondrial disorders.[14] Genetic sequences that contribute towards mitochondrial dysfunction in these children are highly likely to be on the mtDNA as probable maternal inheritance is present in six of our seven pedigrees (fig 1 and see supplementary data). It is well established that individuals with maternally inherited mitochondrial disorders owing to mtDNA mutations demonstrate highly variable expressivity of multiple, protean clinical manifestations, even among relatives in a family carrying the same mtDNA mutation in all of their mitochondria (homoplasmy).[11 12] In accordance with this, none of our eight subjects had CRPS-I as the only clinical manifestation, but all suffered from various other autonomic-related conditions, most frequently bowel dysmotility, chronic fatigue, cyclic vomiting, gastroesophageal reflux, migraine headaches and temperature instability (table 2). Other, non-autonomic, neurological and endocrine disease manifestations were noted in some cases (table 2).

In our clinical experience, chronic, intermittent and moderate-to-severe episodes of limb pain, essentially indistinguishable from the mild episodes seen in our eight CRPS-I subjects, are not rare among children and their matrilineal relatives in families with maternally inherited mitochondrial disease. Although rarely the focus of investigation, these symptoms have been reported before in patients with mitochondrial disease, often being labelled as "neuropathy."[18] In our experience, it is the preponderance of "functional", often intermittent, conditions and ill-defined symptoms, such as muscle pain, in the identified patient and among the matrilineal relatives that often first suggests the presence of mitochondrial disease (fig 1).

As CRPS-I itself is an autonomic-related condition,[1 3] and dysautonomic and other functional/neurological conditions are common among our CRPS-I patients (tables 1 and 2) as well as in the matrilineal relatives who share their mtDNA sequences (fig 1), the investigators propose that CRPS-I can be one of many autonomic manifestations associated with maternally inherited mitochondrial dysfunction (a "maternally inherited dysautonomia"). In this hypothesis, the mtDNA sequence results in a mild-to-moderate degree of mitochondrial dysfunction that predisposes all individuals in the family with the same mtDNA sequence towards the development of multiple autonomic, functional and other neurological conditions, including CRPS-I. This hypothesis has been previously presented in regards to the pathogenesis of cyclic vomiting,[12 19–21] a condition that was present in four of our present children with CRPS-I and a sister from the sibling pair. Within the matrilineage, who will and who will not develop CRPS-I is probably dependent upon additional modifiers, including nuclear genetic (chromosomal genes), environmental, psychological and social factors.

In our anecdotal clinical experience, the signs and symptoms of CRPS-I in our patients generally responded quite favourably to the same multidisciplinary approach employed in patients with mitochondrial dysfunction suffering from other autonomic-related manifestations, such as migraine and cyclic vomiting.[22] In particular, co-enzyme Q10 (gel capsules or liquid

What is already known on this topic

- Complex regional pain syndrome type I (CRPS-I), previously known as reflex sympathetic dystrophy (RSD), is an idiopathic condition characterised by localised, abnormally intense and prolonged pain, allodynia and autonomic changes. It usually appears following a "noxious" trigger such as trauma or surgery.
- Mitochondrial disease can present in a variety of clinical manifestations, but perhaps most common is intermittent disease of nerve and muscle, including dysautonomic and functional conditions. The mitochondria contain their own DNA that is inherited from mother to child without recombination and thus is "maternally inherited".

What this study adds

- In a tertiary-care paediatric genetics clinic, for eight out of eight children with CRPS-I it occurred in conjunction with additional dysautonomic/functional symptoms, especially gastrointestinal dysmotility, migraine, cyclic vomiting and chronic fatigue. All eight met established criteria for mitochondrial disease, and six out of seven families met criteria for maternal inheritance. Our anecdotal experience suggests efficacy with "mitochondrial-directed" treatments.
- Mitochondrial disease should be considered in children with CRPS-I and other dysautonomic conditions. CRPS-I should be considered in patients with mitochondrial disease who complain of idiopathic pain.

preparations, 10 mg/kg/day, maximum 300–500 mg/day, in two divided doses), L-carnitine (100 mg/kg/day, maximum 2–3 g/day, in two divided doses), riboflavin (100–400 mg/day), amitriptyline (highly dose dependent, generally at about 1 mg/kg/day), frequent feedings (three meals and three snacks a day (the "3+3 diet"), fasting is often not tolerated), and exercise/avoidance of immobilisation is employed. In acutely ill patients, intravenous administration of 10% dextrose-containing intravenous fluids at 1.5 times the usual rate is often beneficial. Mitochondrial "failure" can be monitored by serial serum anion gap and urine ketone (standard dip sticks) measurements. Clinical trials are necessary to validate our observations; however, these treatments are considered to be relatively safe and are in general use in the treatment of mitochondrial-related disorders and conditions. Co-enzyme Q10[23] and riboflavin[24] have been shown in double-blind studies to be effective against migraine, a condition present in 5/6 of our cases who were able to verbalise pain, as well as having been associated with mitochondrial dysfunction in many studies.[25] Exercise, a treatment employed in the treatment of CRPS-I, improves mitochondrial oxidative capacity in individuals with and without mitochondrial disease.[26] Furthermore, tricyclic antidepressants, the group of drugs that includes amitriptyline, have multiple known effects on mitochondria, including uncoupling oxidative phosphorylation.[27]

Our observations are limited by the specialised ascertainment in a genetics practice, the small number of patients and the absence of definitive methodology to confirm low degrees of mitochondrial dysfunction and maternal inheritance. In particular, there are no published methods for determining maternal inheritance other than that from our group.[15 17 20] Our current quantitative pedigree analysis is a modified version of those previous methods, but it accounts for differences in the number of relatives on each side of the family. Although our methods lack careful validation, clearly there are statistically significant pedigree-based differences between our CRPS-I and control groups suggesting maternal inheritance in CRPS-I (fig 2, see supplementary data).

In conclusion, within the context of one tertiary-care paediatric genetics practice, CRPS-I was predominately seen in children with a wide variety of other autonomic and non-autonomic-related symptoms in which maternally inherited mitochondrial disease/dysfunction is highly suggested. As CRPS-I is essentially an idiopathic condition, a possible association with mitochondrial dysfunction and/or maternal inheritance warrants further investigation, especially since mitochondrial dysfunction responds to treatment. It is assumed that noxious environmental factors such as trauma or surgery serve as a trigger for the development of CRPS-I in genetically predisposed individuals. The investigators propose that this genetic predisposition is due in part to mtDNA-sequence-mediated mitochondrial dysfunction. These findings suggest that mitochondrial disease and maternal inheritance should be considered in children with CRPS-I who present with other manifestations of dysautonomia and/or neuromuscular disease. However, studies have not been performed on whether mitochondrial dysfunction and/or maternal inheritance are factors in cases with isolated paediatric CRPS-I, adult CRPS-I or in cases ascertained outside of a genetics/metabolic practice. Conversely, children with mitochondrial disorders who complain of chronic and intense idiopathic pain should be evaluated for CRPS-I.

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