

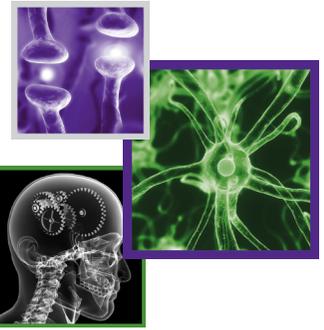
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# Managing cognition in progressive supranuclear palsy

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## Practice points

### Cognitive dysfunction

- Cognitive impairment is integral to progressive supranuclear palsy (PSP).
- The most common impairment is a frontal dysexecutive syndrome.
- PSP may also affect memory, visuospatial function and emotional recognition.

### Behavioral changes

- Behavioral changes can occur early in PSP.
- Apathy and impulsivity commonly co-exist in people with PSP.
- Emotional lability may complicate the diagnosis of depression.

### Medication

- Side effects of levodopa can worsen cognition in PSP.
- Amantadine can be helpful to improve some cognitive aspects including alertness and motivation, but may also cause hallucinations, insomnia and exacerbate impulsivity.
- Anticholinergic medications to reduce saliva production and for urinary symptoms should be selected carefully to limit cognitive side effects.
- Antidepressant medication should be chosen to limit side effects and antipsychotic medications should be avoided if at all possible.

### Educational & behavioral interventions

- There is limited evidence to guide specific interventions.
- An individualized management plan is likely to be the optimum approach.
- Carer education and support is important in managing the cognitive and behavioral aspects of PSP.

### Involving people with PSP in decisions

- Optimizing communication and cognition enables people with PSP to be involved in decisions about their life and health.
- PEG tube insertion and end of life care are two common areas for discussion.
- Early discussions and better integration with palliative care services can facilitate decision-making.

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Cognitive impairment is integral to the syndrome of progressive supranuclear palsy. It is most commonly described as a frontal dysexecutive syndrome but other impairments include apathy, impulsivity, visuospatial and memory functions. Cognitive dysfunction may be exacerbated by mood disturbance, medication and communication problems. In this review we advocate an individualized approach to managing cognitive impairment in progressive supranuclear palsy with the education of caregivers as a central component. Specific cognitive and behavioral treatments are complemented by treatment of mood disturbances, rationalizing medications and a patient-centered approach to communication. This aims to improve patients' quality of life, reduce carer burden and assist people with progressive supranuclear palsy in decisions about their life and health, including discussions of feeding and end-of-life issues.

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## KEYWORDS

- carer education • cognition
- palliative care • PEG
- progressive supranuclear palsy

Progressive supranuclear palsy (PSP) usually affects cognitive function [1,2], despite the emphasis on motor deficits in the diagnostic criteria [3]. Cognitive impairment has a negative impact on the quality of life for people with PSP and their caregivers [4,5]. In this review we outline the main cognitive and behavioral changes encountered in PSP (see also Burrell *et al.* [2]) and consider the beneficial and detrimental effects of medications on cognition and behavior. We then present the evidence to support specific therapeutic intervention, and highlight the benefits of optimizing cognition to enable people with PSP to take an active role in decisions about their life and health.

The clinical syndrome of PSP was first described in 1964 [6], consisting of axial rigidity, akinesia, postural instability, pseudobulbar palsy, slow saccadic eye movements and a supranuclear gaze palsy [1,7,8]. In this review we will focus on the 'Richardson syndrome' or classical presentation of PSP. Other subtypes of PSP have been proposed based on differing initial presenting symptoms or respective review of post mortem cases of PSP. These subtypes include behavioral-onset PSP [9], Corticobasal Syndrome (CBS-PSP) [10], Progressive Akinesia with Gait Freezing (PAGF-PSP) [11,12] and Primary Progressive Aphasia (PPA-PSP) [13]. In addition, there is a substantial body of patients with neuropathological evidence of PSP but who clinically resembled Parkinson's disease (PD) ante mortem (PSP-P, a dopamine-responsive asymmetric syndrome [14]). The underlying pathology in these subtypes is difficult to predict, whereas the Richardson syndrome is associated with the pathological disease of PSP in over 90% of cases [15]. We, therefore, focus on the most common and typical Richardson syndrome of PSP,

but because cognitive syndromes may overlap between PSP subtypes a similar approach to the concepts we discuss here may be applicable in other PSP syndromes.

The pathology of PSP is characterized by the accumulation of tau, a microtubule-associated protein. Hyperphosphorylated tau with four repeats of exon 10 form intracellular aggregates, including neurofibrillary tangles [16]. These tau aggregates are most densely deposited in the subthalamic nucleus, substantia nigra and internal globus pallidus, but are also formed widely in cerebellar and cortical regions [17]. Tau pathology is associated with rapid atrophy in subcortical structures and the midbrain [18,19] with moderate atrophy in frontal cortex [16]. This cortical and subcortical atrophy, and associated neurotransmitter deficits underlie the cognitive deficits of PSP.

## Cognitive dysfunction

The pattern of early cognitive change in PSP is typically summarized as a dysexecutive frontal syndrome [2,20,21]. This may manifest as difficulty with planning and organization and can be readily assessed at the bedside using tests such as the frontal assessment battery [22], verbal fluency [23] or neuropsychological tests such as Trail Making Test B or Brixton spatial anticipation test [24]. Slowness of cognitive processes, including slow speed of processing, is characteristic of PSP, and has been termed bradyphrenia.

Verbal fluency can be simply measured as the number of words generated in 1 min either within a category (e.g., animals) or beginning with a chosen letter (e.g., p-words). The striking deficit of letter fluency can aid the distinction of PSP from idiopathic PD; we have shown that patients who produced fewer than seven p-words

in a minute were much more likely to have the syndrome of PSP rather than PD with a positive predictive value of this simple test alone of 0.81 and a negative predictive value of 0.93 [25]. Using the Frontal Assessment Battery and other tests of frontal lobe function, cognitive impairment is readily detectable at diagnosis but changes little over 12 months [24]. These findings suggest that frontal cognitive impairments are well established early in the disease process.

Frontal executive and verbal fluency changes are observed in most people with PSP, but other cognitive functions can be affected. Many people with PSP perform well on memory tests if they are given sufficient time to complete the test, but memory function can be affected [2] and may predict the level of disability better than other clinical features [26]. The mechanism of memory dysfunction may be related to frontal lobe pathology [21] distinct from the cholinergic mechanisms contributing to memory impairment in Alzheimer's disease. This hypothesis is consistent with the finding that cholinesterase inhibitors are not effective in PSP [27]. The domain of visuospatial function is often impaired in people with PSP [24,26], though may be overlooked in the context of other more striking changes.

Language deficits such as a progressive nonfluent aphasia (PNFA) may be the first presentation of PSP [13], or can appear later in the disease course. Changes of PNFA include agrammatism and impaired comprehension of syntactically complex sentence structure that may limit verbal interaction. Furthermore, communication may be affected by severe hypophonia and dysarthria in the later stages of disease.

Recently, a severe effect of PSP on emotional and social cognition has been recognized [28], not dissimilar to patients with another neurodegenerative tauopathy called frontotemporal dementia (FTD) [29]. This change in emotion recognition and understanding the intentions of other people will exacerbate the communication and behavioral problems that significantly contribute to the loss of quality of life for both patients and their carers.

### Behavioral changes

Changes in personality and behavior are often reported by carers, and confirmed by formal assessment tools such as the Cambridge Behavioral Inventory [30] or the Neuropsychiatric Inventory [31]. Behavioral changes may occur

early in PSP, and a behavioral or 'frontal' presentation accounts for about 20% of all cases of PSP [9]. Behavioral changes are often apparent to families but are rarely reported by people with PSP themselves, a discrepancy that may be attributable to poor insight by patients [32].

In view of the akinesia (slowness of movement) in PSP, it surprises many carers and professionals that people with PSP are often also impulsive [33,34]. This may manifest as motor recklessness, such as getting up to walk despite the high chance of falling and after repeated warnings of the risks involved; or of cramming food into the mouth even while choking. Impulsivity may be accompanied by inflexibility and rigid thinking. Families may describe this trait as stubbornness, selfishness or 'bloody-mindedness', but it reflects damage to the brain circuits between the frontal lobe and basal ganglia that regulate goal-directed behavior and learning [35].

In parallel with this impulsive behavior is an almost universal loss of motivation and apathy [21] that reflects atrophy in medial frontal regions and insular cortex [36]. People with PSP tend not to initiate activities or conversations. This can be a source of frustration for families who may wish to keep their relative 'active' to preserve motor function, and can impair compliance with therapeutic interventions such as physiotherapy or speech exercises. In other neurodegenerative diseases apathy has been associated with increased carer distress [37–39], more rapid disease progression [40] and poorer prognosis. Reports of apathetic behavior from carers may be due to other factors. For example physical disability in PSP may lead to reduced spontaneous movement and goal directed behavior; facial hypomimia may be mistaken for lack of interest. Similarly, apathy may be mistaken for depression which may explain the marked differences between studies in the estimated rates of depression in PSP, ranging from 16% [21] to 56% [41]. However, while apathy and depression may coexist, they are distinct neuropsychological constructs [42]. Many apathetic patients will describe their own mood as good or happy and assert that they do still enjoy things. This contrasts with the perception of a lack of motivation and enjoyment observed by others. In our experience depression *per se* is relatively uncommon in PSP while apathy in the absence of persistent low mood is present in the majority of cases.

Contributing to these behaviors, the maintenance and recognition of emotions may also

change in PSP. Emotional lability is a common symptom, characterized by relatively brief outbursts of emotion such as crying at a sad news story, or laughing inappropriately.

### Medication

The cognitive and behavioral features outlined above are a consequence of the underlying neuropathology in PSP, but may be exacerbated by treatments for the movement disorder and other symptoms of PSP. Levodopa and other dopaminergic medications are trialed in most people with PSP. In clear contrast to the sustained good response in PD dopaminergic medication is generally not effective in PSP, although may have a modest effect for a period of time in a minority of cases [43]. While the focus of most trials of dopaminergic therapy in PSP has been on the motor aspects of the disease, the cognitive effects of levodopa have mainly been studied in PD, demonstrating a nonlinear U-shaped association between cognitive function and dopaminergic medication that is influenced by the stage of disease [44,45]. While the effect (if any) of dopaminergic therapy on cognition in PSP is unclear, in PD smaller doses may improve performance on tasks of cognitive set shifting, but higher doses ‘overload’ the decision and motivation systems leading to impulsivity. The overload of these systems contributes to medication-related impulse control disorders which are relatively common in PD (10–15% [46]) compared with PSP, although there are a few case reports of dopamine-induced impulse control disorders in PSP [47].

Amantadine is also used in PD [48], with a variety of pharmacological actions, including NMDA antagonism [49]. Although there have been no clinical trials in PSP, we have often used amantadine in people with PSP, not only for its potential effect on akinetic rigidity but also to improve alertness, motivation, speech and balance. In a recent audit of cases, we assessed the effect of amantadine in 30 patients with PSP 57% self-reported one or more benefits from amantadine, with more likelihood of benefit in younger and milder patients [YATES T ET AL., UNPUBLISHED DATA]. The benefits we found were related to motor function in nine subjects (two each with improved balance, speech, stiffness, tremor; one with walking), seven nonspecifically felt better and one had markedly reduced fatigue. Adverse reactions to amantadine were common but rapidly resolved on dose reduction: two patients developed hallucinations or aggressive

behavior requiring early drug cessation; three patients, deriving no benefit, reported mild hallucinations and withdrew treatment; four developed hallucinations that resolved with reduced dosages and continued to benefit. Dose reduction abolished gastrointestinal disturbances in two cases, and insomnia and nonspecific unwellness in one case each. Mild livedo reticularis may also occur. In a single case study amantadine has been associated with myoclonus in PSP [50]. Our approach is to start on a low dose, 100 mg once daily, and escalate slowly over 2 months to a maximum dose of 200 mg twice daily or less according to tolerance, having carefully briefed the patient and carer about side effects.

Other common medications may have significant cognitive side effects, particularly the antimuscarinic medications used for incontinence, urgency and urinary frequency, and for other symptoms in PSP such as drooling (sometimes wrongly termed excessive saliva production). For example, Hyoscine is commonly used to reduce salivation but its systemic effects include confusion, unsteadiness and complaints of ‘muzzy-headedness’. Atropine drops used sublingually may be a better local treatment to reduce saliva production, with fewer systemic or cognitive side effects. There is limited evidence to support the use of tiroprium or darifenacin to treat bladder symptoms in people with neurodegenerative diseases as they cross the blood–brain barrier in smaller concentrations than alternatives [51,52], while noncholinergic approaches (e.g., Mirabegron) offer potential advantages.

There is a role for antidepressant medication in PSP to address mood disturbance which can affect cognition and behavior. However, before treatment of depression, one must ensure that the patient actually has a mood disorder. Apathy and facial hypomimia may falsely be interpreted as depression, while high scores on screening tests (e.g., the Beck Depression Inventory, the Hospital Anxiety and Depression Scale) may not reflect a mood disorder, but physical symptoms of PSP such as changes in sleep, weight, libido and fatigue. We suggest asking a patient specifically about their mood in concrete terms and closed questions, for example, ‘do you feel happy’ and ‘do you feel sad’. Although there is no clinical trials evidence to guide selection of any particular antidepressant in PSP, we often use citalopram for a rapid effect and low side effect profile. There is limited support for this approach from trials of selective serotonin

reuptake inhibitors (SSRIs) in FTD where a systematic review and meta-analysis found that antidepressant treatment results in a 15.4 point reduction on the Neuropsychiatric Inventory with the strongest evidence for SSRIs, although acknowledging that the evidence was derived from small trials [53]. Furthermore, enhancing serotonergic transmission with citalopram may have an effect on response inhibition systems in FTD [54]. Trazadone is also well tolerated in people with neurodegenerative diseases [55,56] while Mirtazepine can promote sleep and the maintenance of weight which may be of benefit in PSP. A single case report suggests that repetitive transcranial magnetic stimulation is safe and may be effective for treatment-resistant depression in PSP [57]. Psychosis is rare in PSP, and there should be a high threshold for use of any antipsychotic medication given the evidence that long-term antipsychotic medication increases mortality in people with neurodegenerative disorders [58] and may worsen extrapyramidal syndromes.

There is a particular catch in the diagnosis of depression in PSP; the phenomenon of emotional lability or emotional incontinence. This causes patients to suddenly, and intensely cry and appear distressed, often for a short period (less than a minute). The patient's inner mood state may be very different from the external appearance. SSRIs are often effective for treating emotional incontinence, even in the absence of depression and often at lower doses than typically used to treat depression (e.g., citalopram 10 mg once daily).

Cholinesterase inhibitors and memantine have been successful medications for addressing cholinergic deficits in Alzheimer's disease, but have failed to show the same effect in PSP. An observational study of Rivastigmine in five people with PSP found a small improvement after 3–6 months in verbal fluency and backward digit span [59], but these results should be treated with caution since the study was small and unblinded, and there was a decline in all other cognitive assessments. There has been only a single randomized control trial of a cholinesterase inhibitor in PSP [27]. This trial assessed 21 patients over 6 weeks and found a deterioration in motor function and ability to carry out activities of daily living with only a small effect on memory.

Apathy is a particularly prominent cognitive feature of PSP and is a significant cause of patient morbidity [60,61] and (in other neurodegenerative

conditions) has been linked to significant carer distress [62]. This makes it an attractive target for symptomatic therapy; however, evidence for particular pharmacological treatments of apathy in PSP is limited. In a double-blind randomized placebo controlled trial the GSK-3 inhibitor tideglusib had no effect on apathy (measured by the Straskiein scale) among patients with PSP at 52 weeks [63]. In other conditions, there is limited evidence to suggest modest effects of cholinesterase inhibitors improve apathetic symptoms in dementia [64,65], PD [66] and traumatic brain injury [67]. Dopamine agonists have been used following stroke [68] and in case reports amantadine [69] and selegiline [70]. The stimulant modafinil showed some improvement in apathy in Alzheimer's disease in a double blind placebo controlled trial [71] but another randomized trial showed no effect [72]. Dramatic improvement in the symptoms of PSP (including apathy) has been reported with the GABA agonist zolpidem in an individual case [73] but further evidence is lacking. Because apathy is not a single unitary construct but reflects multiple neuropsychological processes associated with disruption of a number of prefrontal and basal ganglia circuits [74] it is not clear which (if any) of these interventions are likely to be effective in the treatment of apathy in PSP.

Recent efforts to find a disease-modifying treatments for PSP have focused on disrupting the aggregation of hyperphosphorylated tau species. Trials have failed to show any significant effect on disease progression, including cognitive measures, for sodium valproate [75], davunetide [76], tideglusib [63] or riluzole [15]. However, a series of new disease-modifying treatment trials are under way or planned, including immunotherapies. Within 5 years, the scope for disease modification may be much improved.

In the recent years, rasagiline, a monoamine oxidase inhibitor, is suggested to have a disease modifying effect in idiopathic PD in the ADAGIO trial, although a positive result was seen only in the lower dose arm of the study [77]. A trial of rasagiline in 44 patients with PSP showed no effect on disease progression measured by the PSP Rating Scale [78].

### **Educational & behavioral interventions**

Given the limitations of medication in managing cognitive and behavioral symptoms in PSP, non-pharmacological interventions should be the first line of treatment. These interventions are likely

to have few side effects, but may require additional personnel and resources to implement, including education and support for caregivers. Confidence in the diagnosis, and education about the illness can in itself make a significant contribution. Understanding that personality and behavioral change are a result of PSP and not intentional callousness or selfishness can go a long way to reducing the problems they cause.

Limited evidence exists for nonpharmacological interventions across different neurodegenerative disorders [79]. In PSP, evidence supporting general rehabilitation approaches are limited to a few case studies [80], and we are unaware of any published interventions specifically targeting cognition in PSP. A study providing individual assessment for 153 people with Alzheimer's disease followed by a considered intervention reduced behavioral symptoms and carer distress with follow-up over 18 months [81]. Interventions included cholinesterase inhibitors or memantine, communication skills education, caregiver coping skills, legal and finance advice, exercise and a caregiver guide. The study team assigned a specialist nurse embedded in a multidisciplinary team and in close partnership with caregivers. Such a framework is likely to be the optimum approach across neurodegenerative disorders, although crucially the interventions did not improve scores on cognitive tests. Despite this caveat, we believe that the end point of any intervention should be relevant to the quality of life rather than aiming to improve cognition and therefore the measurement of cognitive scores should be a secondary consideration when planning or evaluating such a study.

Translating individual interventions between different neurodegenerative diseases can be problematic. For example, disorientation and memory symptoms that are common in Alzheimer's disease are less prominent in PSP, and impairment of motivation, movement and communication may limit people with PSP participating in activities that may be of benefit in other types of dementia.

The assessment of cognition and behavior should include multiple sources of reference. Clinicians and formal assessment tools may be useful to identify underlying cognitive changes but may not easily translate into meaningful outcomes in the real world. Patients often lack insight into their own behavior and disability; carers, despite being best placed to report

problematic behaviors in the day-to-day setting, may also misinterpret the patient's motivation or behavior, or project their own preconceptions or distress on the patient.

There is emerging evidence to guide the support of caregivers, although clinical trials are needed. A telehealth intervention has been proposed to educate caregivers of people with PSP, although this was not particularly targeted at cognition and its efficacy has yet to be established [82]. A review of psychological input for family caregivers in other neurodegenerative diseases found mainly poor quality studies, but some evidence to support interventional Behavioral Management Therapy at an individual level rather than in a group environment [83]. These findings further support the benefit of individualized, tailored interventions for people with PSP and their carers. In this review, there was no evidence to support the education of caregivers alone. However, rarer forms of dementia such as PSP might be a special case. Specific education has been highlighted as a need for carers of people with FTD in comparison to those caring for people with Alzheimer's disease [84,85].

We propose a set of general principles for approaching behavioral disturbance in PSP (**Box 1**). These principles recognize the unique behavioral challenges in PSP while drawing on aspects neurodegenerative disorders more generally. Further studies are urgently needed to provide guidance in managing specific behavioral symptoms to guide caregivers and professionals in this difficult area.

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### Involving people with PSP in decisions

An important goal of maximizing cognition and communication is to involve people with PSP in decisions about their life and healthcare. To demonstrate the importance of improving cognition in PSP, we will discuss two areas for decision-making with which medical teams are often involved: inserting a percutaneous endoscopic gastrostomy (PEG) feeding tube; and end of life decisions.

Considering a PEG in people with PSP is common since swallowing problems usually develop during the course of PSP, leading to a risk of aspiration pneumonia, weight loss, unpleasant choking episodes and lengthy mealtimes. Although a PEG tube does not prevent aspiration pneumonia, it can have benefits in terms of maintaining nutrition and comfort and

**Box 1. Principles of behavioral management in progressive supranuclear palsy.**

- Gather information on behavior from multiple sources, for example the patient, family, professional caregivers, therapists
- Specific education for caregivers about the cognitive and behavioral spectrum of progressive supranuclear palsy, particularly apathy, impulsivity and emotional lability
- Address systemic causes of behavioral change, for example infection, constipation, pain
- Reduce medication where possible that may cause cognitive impairment, drowsiness or hallucinations
- Low-dose selective serotonin reuptake inhibitor may help to treat emotional lability

does not preclude eating for pleasure. There is a lack of evidence to help with the timing of PEG placement, although studies in motor neuron disease support early placement since waiting until there is significant weight loss, malnutrition and dysphagia increases postprocedure mortality [86], though practice varies between centers on optimal timing for PEG placement. Many people with PSP do not wish to have a PEG tube for cosmetic reasons, concerns about the insertion procedure or because they do not like the idea of ‘artificial feeding’. Patients may also misunderstand the palliative role of PEG, rather than prolonging life *per se*.

Similarly, discussions around end of life care are sensitive and often very personal. These include decisions about where to die, whether to be admitted to hospital to treat infections and resuscitation status. Poor communication between neurologists and palliative care teams may hinder such discussions [87] and a recent survey across the UK highlights the variability between regions in the integration of neurology and palliative care services in PSP and other neurological disorders [88]. We advocate early discussions about palliative care issues and early involvement of palliative care teams to assist with advance care planning in PSP. It may not be comfortable for the clinician to talk about death, fear of death, the processes of dying, and guilt about surviving carers, but patients may be pre-occupied and worried by these issues. Clarifying their concerns reduces the risk of making false assumptions and can enable reassurance and practical measures to be put in place.

In the early years of PSP around the time of diagnosis, the majority of people with PSP will have the communication and cognitive abilities to discuss PEG placement and end of life decisions. Later on in the disease this legal process may need facilitating by a careful assessment of capacity, maximizing cognitive function and optimizing communication.

To properly involve people with PSP and impaired cognition in these important decisions

takes time and patience. A discussion that may take a few minutes with a healthy person can take half an hour in someone with PSP. Our experience is that this is time well spent, and a clearly documented discussion can pave the way for clear decision-making in moments of crisis. There is some evidence that Lee Silverman exercises, designed to address hypophonia in idiopathic PD, can be of benefit in promoting communication in PSP [89]. Further specific guidance for improving communication in PSP is greatly needed but currently lacking [90]. In addition to the medical and nonmedical measures to improve cognition outlined in preceding sections, the environment in which a decision is made can be optimized to assist decision-making [91].

Supporting these decisions within a legal framework can add an additional level of protection for an individual’s wishes [92]. In the UK the Mental Capacity Act 2005 provides the framework within which these decisions are made, although the implementation of the Act by neurologists is variable [93]. The Mental Capacity Act makes provision to appoint a lasting power of attorney, whereby a person of sound mind can nominate someone to take on financial and medical decisions if they become incapacitated at a later date. In addition, an individual can make more specific statements to refuse care, given a certain set of circumstances written down as advanced statements, or more formal legal documents called advance directives.

### Future perspective

In 5–10 year’s time we hope that cognitive dysfunction in PSP will be recognized as a core feature in revised diagnostic guidelines. We would like to see the standard evaluation of a person with PSP to include a formal assessment of cognition, and the standard treatment to begin with formalized education of carers about cognitive issues. We expect that increased awareness of the Mental Health Act and the

growth of neuropsychiatric care will lead to better integration between neurologists and palliative care physicians enabling better optimization of cognition and communication to facilitate advanced care planning and avoiding crisis situations.

### Conclusion

In conclusion, the Richardson syndrome of PSP is associated with many cognitive and behavioural changes, including apathy, impulsivity and a frontal dysexecutive syndrome. Cognition can be worsened by side effects of common medications. There is little clinical trials' evidence to guide the management of these symptoms, but here we set out the rationale and strategies for treating mood disturbance, educating patients and their caregivers, and the benefits of involving people with PSP in decision-making about their life and health.

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# Toward an etiology-based management of trigeminal neuralgia



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“It is not unreasonable to think, for example, in light of recent advances in multiple sclerosis, that disease-modifying therapy may be available for many patients, inevitably leading to neurosurgical treatments left for only the most resistant cases.”

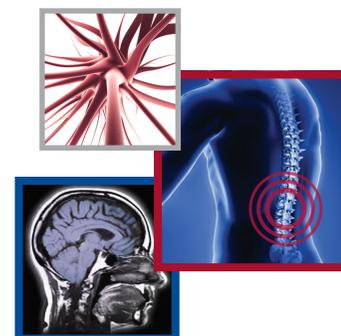
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Despite its relative rarity, trigeminal neuralgia (TN) is well known by the medical community, not the least because of the location and stereotypic presentation of the pain. As first described in detail over 200 years ago [1], the key features difficult to miss are short-lived pain intense paroxysms, set off by innocuous mechanical stimuli, their abrupt onset and cessation, and the presence of trigger zones within the central mask [2]. Among chronic pain conditions, TN stands out as one of the very few whose treatment outcome is measured by the proportion of patients in complete or nearly complete remission. Moreover, there is an abundance of treatment options available, which range from medication to percutaneous neuroablative procedures to intracranial surgery [3–5]. While patients are usually commenced on medication, the lack of effect or poor tolerability is not disastrous, because a suitable intervention can usually be found, irrespective of the patient's age, comorbidity or acceptance of risk. For someone undergoing microvascular decompression (MVD) for their TN,

the likelihood of their neuralgia still being controlled in 10 years of time is over 70%, and for many of those in whom the pain recurs, a repeat posterior fossa exploration or a percutaneous neuroablative procedure (PNAP) – that is, balloon compression, glycerolysis and radiofrequency lesioning of the trigeminal ganglion – is likely to guarantee many more years of freedom from their neuralgia [4,6–8]. For those not suitable for general anesthesia or who cannot tolerate the long sitting position after a glycerol injection, less demanding options such as stereotactic radiosurgery (SRS) of the trigeminal nerve root and intracutaneous botulinum toxin A injections are available [8,9]. In this commentary, I will focus on the choice of surgical treatment in an unoperated patient with clinically established TN [2].

### Limited research evidence to support choice of a surgical treatment

None of the above-mentioned procedures have been subjected to an adequately powered randomized controlled trial. Estimates



### KEYWORDS

- microvascular decompression
- MRI • neuroablative • trigeminal neuralgia • trigeminal root

“Among chronic pain conditions, trigeminal neuralgia stands out as one of the very few whose treatment outcome is measured by the proportion of patients in complete or nearly complete remission.”

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of success are based on large observational studies; relatively few are prospective and presented with actuarial data [6–7,10]. Small controlled pilot studies have been carried out on botulinum A and radiofrequency lesioning but with few subjects and short follow-up cannot be used for meaningful comparison [9,11]. Taken together, no Class A level evidence is available to answer the question of which of the many procedures will be the best choice for the patient with TN who does not respond to, or tolerate, pharmacotherapy. The only Cochrane review to date acknowledges this shortcoming, and was unable to provide any recommendation regarding their use [12]. Despite clear preference of advocates of each of the procedures, there appears to be little appetite for controlled trials comparing two or more surgical treatments, let alone actual efficacy trials.

Direct comparisons would help the clinician to judge which of the many surgical options is best for the patient before them. They differ in their demand for preoperative scanning, need for general anesthesia, immediacy of pain relief, time to recurrence, adverse effects, patient acceptability and cost [7–8,12–14]. How the variability of clinical features among patients with TN affects these outcomes is not known. This means that the operator's clinical judgment relies heavily on their past experience and assumptions based on heterogeneous outcome data available. The key opinion leaders' preferences become informal mainstream guidelines that are difficult to question by others, and are susceptible for many types of spin. Unless one has accumulated a substantial amount of data to set up and maintain a new school of thought, novel approaches have a tough time getting a sympathetic appraisal.

At the moment, MVD is the most common surgical procedure carried out for TN in the USA and is performed seven-times to ten-times more frequently than PNAP [14,15]. The latter is far more cost effective than MVD and SRS even after costs per quality adjusted life-year are estimated [14]. The popularity of MVD has steadily increased over the last decades thanks to a large number of reports of long-term results with acceptable mortality and morbidity. Also, the rationale behind it is hard to miss by operators and patients. The concept of a single cause, visualized on preoperative MRI scan which can be removed to restore the normal function of the nerve, is highly persuasive. By contrast, PNAP

and SRS only stop the pain via intentional injury inflicted on the nerve, are associated with a higher risk of adverse somatosensory effects and are not believed to lead to similar long-term pain relief as MVD. This widely held view arises from comparison of data from existing cohort studies with no certainty that they represent identical populations.

The rise in the popularity of MVD hides two caveats. First, some operators fail to acknowledge that the diagnosis of TN is purely clinical. This may lead to undue emphasis given to MRI findings and operations performed on patients with no TN at all, or presenting with atypical features. Second, the exact anatomical relationship, notably the exact site of compression and the intensity of compression, may not feature in the decision to operate or not. Therefore, even if a preoperative MRI does show a neurovascular contact with the symptomatic nerve and it matches the anatomical situation at operation, it does not automatically follow that such a finding has clinical significance. Neurovascular contact is found commonly in patients with other than facial pain conditions (in 84% with trigeminal neuropathy [16]) and in 17–92% of people with no history of TN [17,18]. It is reported impacting on the asymptomatic (contralateral) trigeminal nerve in 35–75% of patients with TN [17,19].

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### Does MRI have a role in guiding the treatment decision?

Given the above confusing findings, where does MRI stand in the assessment of the patient with clinically established TN? To put it differently, can MRI identify the type of change in neurovascular compression (NVC), which, if surgically rectified, leads to the resolution of TN pain? (Of note, reliable detection of NVC requires the use of specific imaging techniques with 3D reconstruction) An early insight into the first question was provided by Sindou *et al.* in a cohort study of 362 patients followed up to 15 years post MVD [20]. Compared with patients with MRI evidence of neurovascular contact only (grade I), those with clear NVC, defined as either showing distortion and/or displacement of the trigeminal root (grade II) or marked indentation in the root (grade III), showed significantly higher rates of successful outcome from MVD at 1 and 15 years. Later, the same group showed that both the location and the degree of NVC could be reliably estimated from a preoperative 3D reconstruction

“...can MRI identify the type of change in neurovascular compression, which, if surgically rectified, leads to the resolution of trigeminal neuralgia pain?”

MRI; with  $\kappa$  values in the range of substantial or near-complete agreement between the radiological and surgical findings [21]. Moreover, there was little disagreement in the interpretations of the imaging results between two independent neuroradiologists [21]. In 2014, another group set out to determine which, if any, MRI findings were specific for TN. They carried out a review of nine prospective blinded case–control studies, including their own, in which the findings on 3D reconstruction MRI of classical TN patients were available for both symptomatic and asymptomatic nerves [22]. Anatomical nerve changes (atrophy, dislocation, distortion, flattening or indentation) were detected in 152 of 286 symptomatic nerves (53.1%) and in 43 of 474 asymptomatic nerves (9.1%), a significant difference ( $p < 0.0001$ ) with an odds ratio of 11.8 (95% CI: 7.8–17.9). In their own substudy of 24 patients, the combined presence of nerve atrophy and compression at trigeminal root entry zone (TREZ) was highly specific for the symptomatic nerve (100%) [22]. However, the sensitivity was only 52%, and together with the intermediate value of negative likelihood ratio (0.5), it means that the absence of this finding on MRI should not be interpreted as prediction that no compression is found at surgery [22].

NVC at TREZ and local atrophy; the latter digitally measured from 3D reconstruction magnetic resonance (MR) images, as the volume of cisternal trigeminal root and cross-sectional area (CSA) at 5 mm from the edge of the pons also stood out as the most common finding in a similar study [23]. The volume and CSA of the root were smaller on the symptomatic side as assessed by two neuroradiologists blinded to patients' clinical details, and agreed with the operative estimates of severity of compression by a neurosurgeon blinded to the imaging results [23]. Atrophic changes were greatest when NVC was located in TREZ at which the compression also was most severe. When the outcome of MVD was assessed at 2 years, those with greatest local atrophy (i.e., reduction of CSA) who commonly had grade II or grade III compression at TREZ remained in remission significantly more frequently than those with lesser or no local atrophic changes [23].

In the absence of decisive controlled trials, the above studies serve as useful proxies [21–23]. The very high percentage of long-term complete pain control after MVD in a carefully chosen patient is arguable at the level where controlled

trials cannot realistically add to the weight of the evidence [24]. Therefore, for the patient, who has classical TN, and whose 3D reconstruction MRI shows major NVC at TREZ and indisputable anatomical changes in the nerve root, MVD can reasonably be considered to be the treatment of choice. Extrapolating from the available published data, some 50–60% of previously unoperated patients with primary TN can be predicted to fall into this category [19,21,23]. The remaining 40–50% will have a lesser or no NVC, or a prominent compression outside TREZ, and a normal looking trigeminal root on MRI. For such cases, the surgical options with claims of successful long-term pain relief include both percutaneous neuroablation and posterior fossa procedures [20,25–26]. From numerous studies published – mostly observational cohort studies or nonrandomized comparisons – it is not possible to draw conclusions as to the superiority of any single intervention.

#### **Need for controlled studies addressing specific research questions**

It would be a pity if the tradition of resistance against prospective controlled trials of surgical interventions for TN were to continue. After the publication of the first case series on MVD by Jannetta in 1967 [27], it took over three decades until the global neurosurgical community had reached a consensus on NVC as the leading cause of TN and MVD and its primary treatment [28]. The present author posits that for the 40–50% of the TN population for which MVD cannot yet be justified as the primary intervention, controlled trials are a rational way forward. The patients could be randomized to undergo either posterior fossa exploration or a selected neuroablative procedure (or procedures). The primary outcome would be time to recurrence of TN at 2 or more years; among many secondary outcomes, safety and cost–effectiveness would feature prominently. If several centers join forces, it is entirely possible to recruit a large enough sample of eligible patients within a reasonable time scale. Percutaneous neuroablative treatments are available in both neurosurgical and non-neurosurgical centers as they are performed by radiologists and pain physicians also, and SRS is available in centers with oncological units. Eligible patients would be previously unoperated and those with paroxysmal pain only; however, there would be no restriction in regard to age, duration of TN or responsiveness

“Percutaneous neuroablative treatments are available in both neurosurgical and non-neurosurgical centers as they are performed by radiologists and pain physicians also, and stereotactic radiosurgery is available in centers with oncological units.”

to carbamazepine or other sodium channel blockers. An undeniable challenge would be the long duration of such a study, but time gained in comparison with the traditional haphazard observational data collection would be substantial in any case.

Meanwhile, the author proposes the following approach for the management of previously unoperated TN:

- It is critically important to remember that TN is a clinical diagnosis. How to clinically establish the diagnosis in a previously undiagnosed and untreated patient is well described in a recent review [2];
- Once TN is established clinically, arranging an MRI is recommended as it provides the best chance to delineate the etiology of TN. It readily identifies tumors, found in up to 10% of patients with no neurological symptoms or signs other than TN [2]. TN is a rare first manifestation of multiple sclerosis (MS); MRI shows demyelinating plaques if T2 sequences are used and preferable imaging covers the whole of the brain stem. The main indication for MRI is to identify a possible NVC;
- The initial management of TN is pharmacological, the choice being between carbamazepine and oxcarbazepine. Although some authors advocate the use of alternative medication, if the two drugs fail, there is very little evidence they work [29]. It is in the author's opinion that as long as the patient is not against any proposal for posterior fossa surgery, or has a serious comorbid condition that presents a contraindication, the MRI should be obtained using sequences that allow 3D reconstruction of images for assessment of a possible NVC. In this way, all treatment options, i.e., pharmacological and nonpharmacological, can be presented to the patient at the outset. Feedback from patients suggests that the consideration for MVD may be unduly delayed [13]. Many patients on medication report adverse effects reducing their quality of life, or may wish to give consideration to an early surgical procedure, even if their pain is controlled. Those seen in secondary or tertiary care services have usually failed pharmacological therapy and are already seeking the option of a surgical intervention;
- From the 3D reconstruction MRI, the location of any compression is determined together

with any atrophy and dislocation of the symptomatic nerve (commercial digital software is available to measure the volume and circumference of the cisternal portion of the trigeminal root). If arterial compression is found at TREZ with evidence of atrophy at compression site, indentation and/or dislocation of the nerve (fulfilling the criteria for classical TN [2]), the preferred treatment is MVD, provided that the patient appreciates not only the high success rate from the operation (an over 70% probability of complete freedom from TN lasting at least 10 years) but also the risks involved;

- If a lesser compression is found outside TREZ, the compression is by a vein, or no associated anatomical changes in symptomatic trigeminal nerve root are seen on MRI (idiopathic TN [2]), any option involving ganglion-level percutaneous ablation or posterior fossa exploration (MVD or an alternative procedure at the operator's discretion) can be considered, with no single approach to recommend for the time being;
- In patients who refuse or have a contraindication for surgical options, SRS is the preferred option. Due to its slowly emerging effect, interim treatment with botulinum toxin A injections may be considered (while ensuring the patient understands that the evidence base for its use in TN is limited).

“It is not overly optimistic to predict that in the near future the proportion of new ‘idiopathic’ trigeminal neuralgia patients will decrease and our understanding of the pathophysiology of trigeminal neuralgia increases.”

### Future perspective

Many clinical reasons justify an increasing use of MRI to improve patient selection and refine operative methods. It is not overly optimistic to predict that in the near future the proportion of new ‘idiopathic’ TN patients will decrease and our understanding of the pathophysiology of TN increases. Even in such promising circumstances, however, many issues remain unresolved and will require determined research. For example, there is no general agreement on the best management of patients with MS who are also shown to have NVC, patients with typical TN paroxysms as well as continuous facial pain between them or exhibiting clear sensory loss or patients with recurrent TN following an initially successful operation. Fortunately, rapid progress is being made with modern neuroimaging methods (e.g., diffusion tensor imaging and tractography), somatosensory profiling, molecular level nerve pathology and genomics. These could be expected to lead more

targeted noninvasive treatments with far more successful pain control than with current drugs. It is not unreasonable to think, for example, in light of recent advances in MS, that disease-modifying therapy may be available for many patients, inevitably leading to neurosurgical treatments left for only the most resistant cases.

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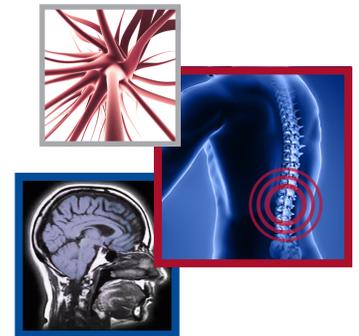
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# Complex regional pain syndrome in children: a systematic review of clinical features and movement disorders

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### Practice points

- Dystonia and movement disorders are still under-recognized in children and adolescents with complex regional pain syndrome.
- This systematic review shows dystonia to affect one in three children and adolescents with complex regional pain syndrome.
- Early detection of movement disorders will help to offer patients appropriate management strategies.
- Multidisciplinary approach is needed in all patients in order to elicit the full picture of the disease.

**Aim:** To ascertain clinical features of complex regional pain syndrome (CRPS) in children with a focus on movement disorders. **Methods:** all publications with original data on children with CRPS were assessed. Data were tabulated and descriptive statistics were applied. **Results:** One population-based study and nine clinic-based studies provided data on demographic and clinical characteristics of childhood CRPS. Mean age of onset was 12.5 years and 85% of patients were females (risk ratio: 1.70; 95% CI: 1.54–1.88). History of trauma in 71% and the lower limbs were affected in 75% of patients. A secondary site involvement was present in 15%. Movement disorders and dystonia were reported in 30% of children. **Conclusion:** Majority of cases of CRPS in children are females with mean age of 12.5 years. Movement disorders (mainly dystonia) affect at least one in three children with CRPS.

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### Background

#### • Definition, epidemiology & classification

Complex regional pain syndrome (CRPS) is a debilitating disorder characterized by a continuous and severe pain affecting one part of the body, usually a limb following an injury. The pain is disproportionate to the intensity of the injury and the tissue damage. The pain is associated with heightened sensitivity to touch and autonomic disturbances such as edema, a change in skin color, a change in temperature and an abnormal circulation.

CRPS is extremely rare in children under 5 years of age and only a few cases are reported in preschool children. The estimated incidence of CRPS in schoolchildren (5–15 years of age) is

### KEYWORDS

- children and adolescents
- complex regional pain syndrome
- dystonia

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1.2/100,000 with a mean age of onset around 12 years. CRPS affects more girls than boys in a ratio of around 3:1 [1].

CRPS follows a minor injury to the affected limb, in the majority of cases, and called ‘CRPS type 1’ (previously known as reflex sympathetic dystrophy). CRPS may follow a peripheral nerve injury and is called ‘CRPS type 2’ (previously known as causalgia). In some patients, no definite history of injury can be identified. If the clinical criteria for the diagnosis of CRPS cannot be fulfilled in its entirety and the patients have a lower number of signs or symptoms or had a previously documented CRPS signs and symptoms, the disease is described as ‘CRPS–NOS’ (not otherwise specified) [2].

• **Criteria for the diagnosis of CRPS**

The diagnosis of CRPS in children is made on fulfilling clinical criteria designed for use in adult patients. There are no specific criteria for use in pediatrics, but most, if not all, studies on CRPS in children have applied these criteria. The International Association for the Study of Pain (IASP) introduced the clinical criteria for the diagnosis of CRPS (Box 1) in 1995 [3]. The Budapest criteria (2007) aimed to reduce diagnostic ambiguity in clinical practice and to improve accuracy in research studies (Box 2) as there are no biochemical tests, biological markers or radiological findings to confirm the diagnosis [4].

• **Movement disorders in CRPS**

Movement disorders (MD) are common complications of CRPS in adult patients. Irregular myoclonic jerks and dystonic muscle contractions were reported in 48% of patient with CRPS type 2 and in 27% of those with CRPS type 1 in a study of 145 adults with CRPS [5]. In another study, 16 out of 58 (28%) adult patients had episodic dystonia and 19 (33%) had constant dystonia [6].

• **Pathogenesis of CRPS**

The pathogenesis of CRPS is not well understood. The suggested mechanisms are not

supported by robust evidence and are likely to be a complex interaction between genetic susceptibility [7] and excessive inflammatory response to injury [8] followed by CNS sensitization [9]. Neuro-inflammatory processes are likely to initiate and maintain the disease process [10]. In patients with CRPS type 1, tissue damage triggers an inflammatory process and the release of several neuropeptides. In cases of CRPS type 2, nerve injury and overstimulation of the sensory nerve fibers may lead to an excessive and uncontrolled release of neuro-inflammatory neuropeptides such as substance P and Calcitonin-Gen Related Peptide. In both types of CRPS, the resultant local and, often, sustained vasodilatation and increased capillary permeability are manifested with the observed autonomic changes in skin color, temperature and edema [10].

The persistent tissue inflammation and the repeated and continuous sensory nerve stimulation may lead to overstimulation of central pain receptors and networks that would induce a state of ‘central sensory sensitization’ in the spinal cord and the cerebral cortex. Such a state of central sensitization reinforces the peripheral responses leading to a state of chronic pain even in the absence of afferent pain stimuli. Functional cerebral MRI studies showed evidence of sensory cortex activation and reorganization of central motor circuits in patients with CRPS [11].

• **Mechanisms of movement disorders**

The mechanisms of movement disorders may involve peripheral and central neurological pathways, but the exact factors involved in the pathogenesis are not well defined and understood. The resulting central sensitization of pain receptors may also trigger abnormal and exaggerated motor responses that are manifested with muscle contraction, spasms, jerks or sustained dystonia [12]. The dystonic posture may involve other limbs on the same or even the opposite side [13].

The occurrence and clinical presentation of MD is poorly studied in children with CRPS. This study aims to review the clinical

**Box 1. International Association for the Study of Pain criteria for the diagnosis of complex regional pain syndrome.**

- Develops after an initiating noxious event (type I) or after a nerve injury (type II)
- Spontaneous pain or allodynia/hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event
- There is or has been evidence of edema, skin blood flow abnormality or abnormal sudomotor activity in the region of the pain since the inciting event
- This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Data taken with permission from [3].

**Box 2. Budapest criteria for the diagnosis of complex regional pain syndrome.**

*The diagnosis of complex regional pain syndrome is made on fulfilling criteria A–D:*

- A. The patient has continuing pain which is disproportionate to any inciting event
- B. The patient has at least one sign in two or more of the categories (all categories in research or trials)
- C. The patient reports at least one symptom in three or more of the categories
- D. No other diagnosis can better explain the signs and symptoms

**Categories**

- Sensory: Allodynia (to light touch and/or Hyperesthesia does temperature sensation and/or also qualify as a deep somatic pressure and/or symptom joint movement) and/or hyperalgesia (to pinprick)
- Vasomotor: Temperature asymmetry and/or if you notice skin color changes and/or skin temperature color asymmetry: must be >1°C
- Sudomotor/oedema: Edema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)

Data taken with permission from [4].

characteristics of CRPS in children with a special focus on MD and their impact on the course of the disease.

**Methods**

An electronic literature search of PubMed, EMBASE, Ovid, Cochrane databases and Google Scholar was carried out, most recently in October 2016. The search command included ‘complex regional pain syndrome’, ‘reflex sympathetic dystrophy’, ‘children’ and ‘adolescents’.

Publications were included in this systematic review if they fulfilled the following conditions:

- Published in English;
- The diagnosis of CRPS is based on either IASP (Box 1) or Budapest Criteria (Box 2);
- Provided original data on children identified through population studies;
- Provided original data on a complete cohort of pediatric clinic population.

Manuscripts were excluded from the systematic review if they were:

- Review papers with no original data;
- Studies on adult patients;
- Reports on single cases;
- Reports on treatment modalities and unusual causes or complications;
- Focused on the psychological aspects of the disease; and

- Focused on disease pathophysiology.

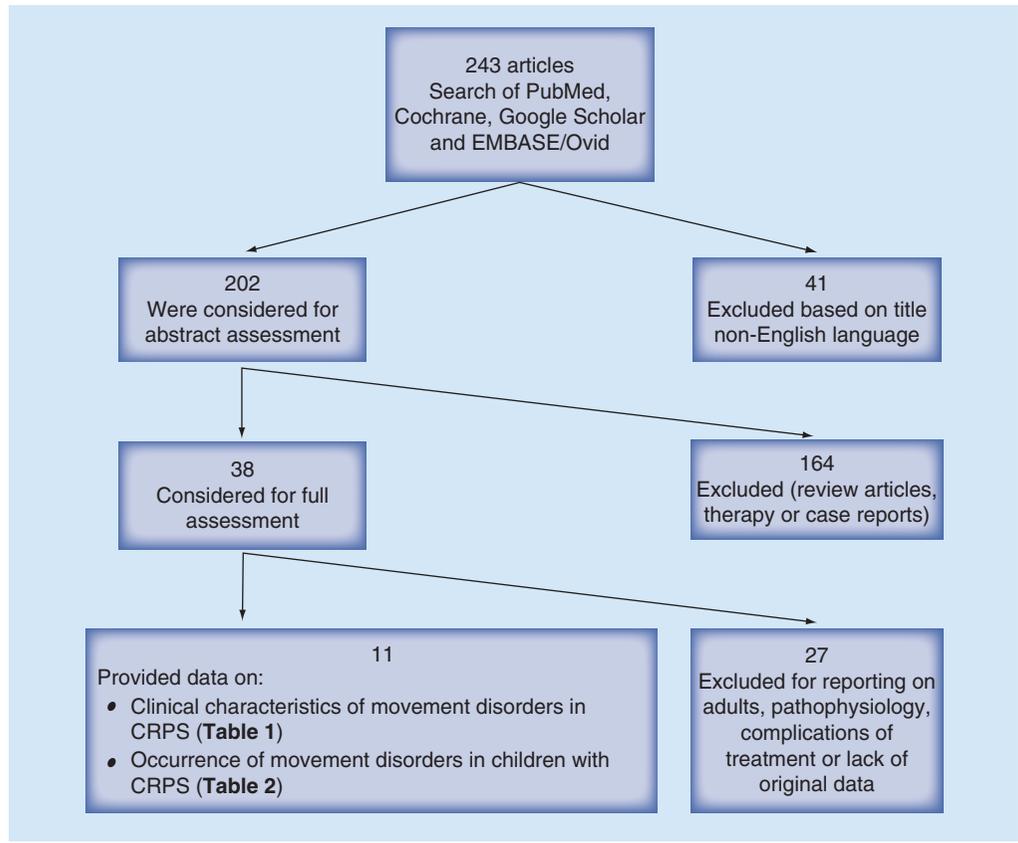
The assessment and evaluation of papers to be included in this systematic review were initially by screening the title and the abstract for inclusion/exclusion criteria followed by full evaluation of the publication:

- Information was collected on patients ages, gender, limb affected, secondary site involvement, movement disorders and dystonia;
- Relative risk for gender predominance was calculated and plotted with its 95% CI;
- PRISMA checklist was used to comply with the systematic review methodology;
- Ethical approval was not necessary and was not sought.

**Results**

Figure 1 shows the search results and exclusion process. 38 papers were studied in full (Figure 1). Eleven papers fulfilled the inclusion criteria. Patients’ demographic and clinical characteristics of CRPS in children were derived from ten studies (Table 1). Data on movement disorders were either missing or incomplete in the studies listed in Table 1 and therefore, the occurrence and the clinical features of movement disorders were derived from two studies only (Table 2). One study provided data for the two tables.

Children with CRPS (Table 1) were reported from different pediatric clinical services including pain management, rehabilitation, rheumatology, surgery, orthopedics and neurology. The mean age of children with CRPS was between 12.5 years and the majority of patients were



**Figure 1. Results of literature search and exclusion process.**  
CRPS: Complex regional pain syndrome.

females (85%). The female predominance was consistently reported in all the studies with an overall risk ratio of 1.70 (95% CI: 1.54–1.88) as seen in (Figure 2). There was a clear preceding limb trauma in 71% of patients (CRPS type 1). The lower limbs were affected in 76% of patients. In 15% of patients a secondary site was reported; 5% on the same side (ipsilateral) and 10% on the other side of the primary site (contralateral).

Two pediatric studies provided full analysis of MD in children with CRPS and the demographic findings are summarized in (Table 2). MD were reported in 20 out of the 58 patients (34%). 16 of the 20 patients with MD (80%) were females and the mean age of patients was 11.8 years. 18 patients with MD (90%) had dystonia, either as the only movement disorder (13 children) or alongside other movement disorder (five children). Only two patients (10%) had MD other than dystonia (Table 2).

Data on the prognosis of CRPS and dystonia varied and there were no homogeneity to allow systematic review of the published

studies. There are only a few published studies with follow-up data on children with dystonia and CRPS that employed variable treatment modalities, making the analysis to determine the natural course of the disease very difficult.

One study reported a follow-up data on ten children for periods between 6 months and 14 years showing a complete resolution of symptoms in four, a slight improvement in two and no improvement in four children [23]. In a study of four adolescent girls with dystonia, psychological comorbidities were reported to play an important role in the pathogenesis and the persistence of fixed dystonia that responded only to psychological intervention in three patients [24].

Reports on treatment of CRPS in children were diverse and there was no consistent single management strategy that could be studied in this systematic review.

### Discussion

CRPS is not uncommon in children and adolescents and thus this systematic review of its

incidence, clinical features and complications, especially in relation to MD and dystonia, is timely and relevant. A systematic review of CRPS in children is also necessary because cases are reported from different pediatric clinical services and settings with a clinical focus on different aspects of the disease and different aspects of its treatment and management.

Review of the available literature provided a number of reliable studies that allowed the analysis of the demography and clinical presentations of the disease. Only two studies provided enough data to allow the estimation of the prevalence of MD and dystonia in children with CRPS. The small number of studies and the small number of patients in these studies are recognized limitations of this systematic review.

• **Epidemiology & demography**

Despite these limitations, it is possible to accept the consistent demographic finding as true reflection of the population of children affected by CRPS. The mean age of onset is shown to be around 12 years and the occurrence of the disease under the age of 5 years is extremely rare. The female predominance is consistent and up to 85% of patients are females.

• **Criteria for the diagnosis of CRPS in children**

This systematic review has shown the consistent use of the IASP and Budapest criteria successfully in children, but it is not possible to confirm the validity of the criteria in the absence of any confirmatory test. However, on the evidence available so far, there is no reason to suggest that the criteria for the diagnosis of CRPS are not equally applicable in children and adolescents. Children present with typical continuous severe pain, which is disproportionate to the injury and is almost always associated with autonomic features and allodynia. The disease runs a chronic course following acute presentation.

Exclusion of other possible diagnoses is necessary and investigations are necessary to exclude infections of skin (cellulitis), connective tissues (fasciitis), muscles (myositis), bone and joints (osteomyelitis and septic arthritis). Radiological imaging (ultrasound, computed tomography, MRI or isotope scans) may also be necessary if inflammatory diseases, fractures, neoplasm and deep venous thrombosis cannot be excluded clinically.

**Table 1. Studies on complex regional pain syndrome in children.**

Study (year)	n	Female	Mean age (year)	Trauma	LL	UL	LL + UL	Bilateral	Disability	Relapse	MD	Dystonia	Clinic	Ref.
Sherry <i>et al.</i> (1999)	103	87	12.7	56	83	10	9	17	83	-	0	0	Rehabilitation	[14]
Murray <i>et al.</i> (2000)	46	35	12.0	25	30	14	2	0	0	0	0	0	Rheumatology	[15]
Sethna <i>et al.</i> (2007)	42	40	13.2	42	42	0	0	0	0	0	1 (tremor)	0	Pain	[16]
Low <i>et al.</i> (2007)	20	18	11.8	16	17	3	-	-	-	3	0	0	Pain	[17]
Tan <i>et al.</i> (2008)	78	67	13.0	66	53	17	3	3	-	22	36 <sup>†</sup>	0	Surgery	[18]
Kachko <i>et al.</i> (2008)	14	10	11.9	12	8	6	0	0	-	4	0	0	Pain	[19]
Bayle-Iniguez <i>et al.</i> (2015)	73	64	11.5	36	65	8	-	18	73	0	0	0	Orthopedics	[20]
Wager <i>et al.</i> (2015)	37	35	14.0	31	15	17	5	0	-	-	0	0	Pain	[21]
Stalla <i>et al.</i> (2015)	7	6	11.0	3	5	2	0	0	-	-	0	0	Neurology	[22]
Abu-Arafeh <i>et al.</i> (2016)	26	19	11.9	20	19	7	5	5	-	0	10	10	Population	[1]
	446	379 (85%)	12.5	317 (71%) <sup>‡</sup>	337 (76%) <sup>‡</sup>	84/404 (21%) <sup>‡</sup>	24/290 (8%) <sup>‡</sup>	43/280 (15%) <sup>‡</sup>	156	25	47	10		

<sup>†</sup>Tremors, spasms, myoclonus and involuntary movements.

<sup>‡</sup>Percentage on studies with eligible data.

LL: Lower limb; MD: Movement disorder; UL: Upper limb.

**Table 2. Studies on movement disorders in children with complex regional pain syndrome.**

Study (year)	Patients CRPS	Female CRPS	Patients with MD	Female with MD	Patients – dystonia	Patients – dystonia and other MDs	MD with no dystonia	Secondary remote sites	Primary site away from CRPS site	Ref.
Agrawal <i>et al.</i> (2008)	32	27	10	8	6	2 (tremors 1, myoclonus 1)	2	2	1	[23]
Abu-Arafeh and Abu-Arafeh (2016)	26	19	10	8	7	3 (spasms 2, jerks 1)	0	1 (dysphonia)	0	[1]
<b>Total</b>	<b>58</b>	<b>46 (79%)</b>	<b>20 (34%)</b>	<b>16 (80%)</b>	<b>13</b>	<b>5</b>	<b>2</b>	<b>3</b>	<b>1</b>	

CRPS: Complex regional pain syndrome; MD: Movement disorder.

It was not possible on this systematic review to establish a consistent and reproducible plan of investigations of children with CRPS and the value of each investigation except for the purposes of excluding other conditions.

• **Clinical features of CRPS in children**

Only one population based study reported on the clinical characteristics of CRPS in 26 unselected children. Other studies reported on children attending different clinical settings

and a bias in reporting cannot be excluded. However, the systematic review looking at all the patients offers a balanced assessment of the clinical findings. Therefore, it is reasonable to accept that three quarters of patients suffer from CRPS type 1 with a trauma varying in severity from minor injury (in most patients) to serious injuries with bony fracture (in some patients).

It is also possible to accept that in at least 70% of patients lower limbs are the primary site of CRPS, which is in variance to the experience in

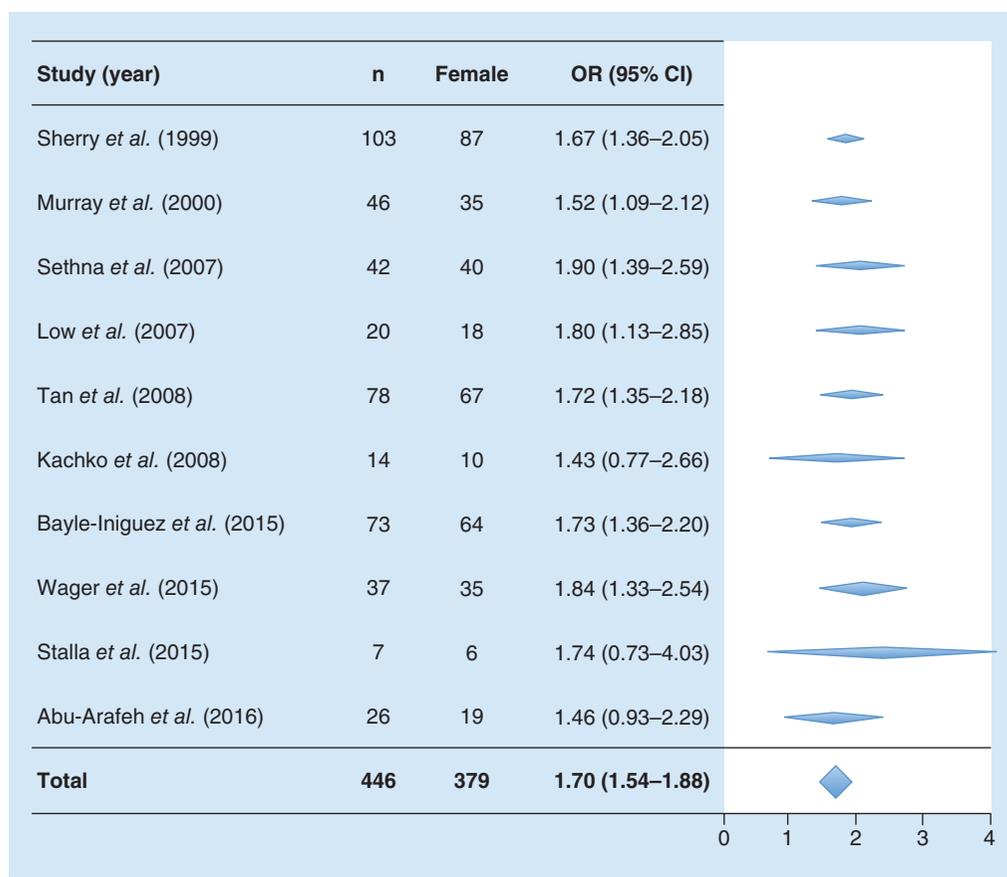


Figure 2. Odds ratio for female preponderance in complex regional pain syndrome.

OR: Odds ratio.

Data taken from [1,14–22].

adults. A population-based study in USA, of 74 adult patients with CRPS, reported the upper limbs to be twice as likely to be affected as the lower limbs [25]. The difference is likely to represent the higher risk of lower limbs injuries in children rather than the difference in the disease itself.

A secondary site was seen in at least 15% of children with CRPS, which is much less than the incidence of a second site in adult patients (48%) as seen in a retrospective study of 184 patients [26]. The smaller number of children with a secondary site involvement is probably due to the shorter course of disease and/or follow-up.

#### • Movement disorders in children with CRPS

This systematic review shows that MD and dystonia may occur in at least a third of patients with CRPS similar to their frequency in adult patient with CRPS. It is not possible to make a more accurate estimate because the diagnosis of MDs and dystonia is based on clinical assessment and neurological findings.

The difficulties in making full assessment of the affected limb can cause under-recognition and underdiagnosis of MD in CRPS. These difficulties are due to the intensity of pain and the allodynia that may mask the neurological signs. Children will be resistant to the touch of the limb and may not allow the physicians to test the muscle tone and range of movements. It is therefore, necessary for these children to be assessed within a multidisciplinary team that includes a specialist in pediatric neurology. Patients with dystonia may show evidence of muscle contracture that will be present even under general anesthesia. There will be a degree of rigidity, abnormal and

exaggerated deep tendon reflexes and loss of function disproportionate to the degree of pain or despite a good pain relief. Dystonia tends to take a chronic course and complicate the clinical picture. A secondary site of dystonia involving a site other than the limb affected with CRPS is not uncommon and in one patient dysphonia was reported as secondary event.

In summary, CRPS in children is a disease of adolescents and up to 85% of patients are girls. One in three children with CRPS may have secondary complication manifested with movement disorder, mainly dystonia.

#### Conclusion

Majority of cases of CRPS in children are type 1 (following injury). Mean age of presentation in children is 12.5 years and the vast majority of affected children are female. The lower limbs are affected in three out of four patients. Secondary site involvement is not uncommon. Movement disorders (mainly dystonia) affect at least one in three children with CRPS. Treatment trials and research is needed to validate the criteria for the diagnosis of CRPS in children.

#### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

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