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Complex regional pain syndrome following immunisation

Stephanie Richards,[1] George Chalkiadis,[2] Raman Lakshman,[3] Jim P Buttery,[1,4,5] Nigel W Crawford[1,4,6]

[1]SAEFVIC, Department of General Medicine, Royal Children's Hospital (RCH), Melbourne, Victoria, Australia
[2]Department of Anaesthetics and Pain Management, Royal Children's Hospital, Melbourne, Victoria, Australia
[3]Department of Paediatrics, West Suffolk Hospital NHS Trust, Suffolk, UK
[4]Murdoch Children's Research Institute (MCRI), Melbourne, Victoria, Australia
[5]Paediatric Infectious Diseases Unit, Department of Paediatrics, Monash Children's Hospital, Southern Health, Monash University, Melbourne, Victoria, Australia
[6]Department of Paediatrics, The University of Melbourne, Melbourne, Victoria, Australia

Correspondence to
Dr Nigel W Crawford, SAEFVIC Immunisation Safety Service, Department of General Medicine, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Melbourne, VIC 3052, Australia; nigel.crawford@rch.org.au

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ABSTRACT

Complex regional pain syndrome type 1 (CRPS-1) is a clinical syndrome that affects one or more extremities and is characterised by persistent pain disproportionate to any inciting event, and at least one sign of autonomic dysfunction in the affected limb(s). The pathogenesis of this syndrome is poorly understood, but its onset is often precipitated by a physical injury, such as minor trauma, fracture, infection or a surgical procedure. In the literature, there are reports of CRPS-1 following immunisation with rubella and hepatitis B vaccines. Here we present a case series of CRPS-1 following immunisation in adolescents, with either diphtheria-tetanus-acellular pertussis (1 case), or human papillomavirus vaccines (4 cases). Enhanced awareness of this syndrome and its potential to occur following immunisation in the paediatric population is vital to the prompt and effective management of this condition.

INTRODUCTION

Adverse events following immunisation (AEFI) commonly include local pain at the injection site, but the development of complex regional pain syndrome type 1 (CRPS-1) has only been described in the literature temporally associated with rubella and hepatitis B vaccines.[1 2] CRPS-1 is a clinical syndrome that affects one or more extremities and is characterised by persistent pain disproportionate to any inciting event, and at least one sign of autonomic dysfunction in the affected limb(s).[3] In the paediatric population, the development of CRPS-1 is often precipitated by minor trauma.[4] There is no definitive investigation for evaluating symptomatic children, and the diagnosis of CRPS-1 is based on history and examination findings. Management of CRPS-1 in children is multidisciplinary, often with an initial focus on physical therapy and encouraging use of the affected limb.[3 4] Clinical judgment and individual assessment through the multidisciplinary team will determine the need for addition of psychotherapy, including cognitive behavioural techniques and pain education and/or medication into the treatment plan to facilitate recovery.[4]

Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC) was established in the state of Victoria, Australia, in April 2007.[5] It is a central reporting enhanced passive surveillance system with associated clinical service for AEFI in children and adults within Victoria. Any AEFI report is reviewed by a specialised immunisation nurse, and contact is then made with the vaccinated person or their guardian to discuss the report and arrange further follow-up as necessary. Reports are subsequently forwarded to the national body, the Therapeutic Goods Administration. All reports of AEFI received by SAEFVIC between May 2007 and December 2009 were selected for analysis. AEFI following any vaccine coded as CRPS, were reviewed, and a secondary review undertaken by a pain medicine specialist (GC). Of the 13 cases identified over this time period, four cases had clinical features consistent with a diagnosis of CRPS-1 as defined by Harden *et al*.[3] A case from the UK (case 4) was identified in 2009 from an international vaccine safety discussion group. The International Association for the Study of Pain criteria for CRPS-1, as adapted from Harden *et* al,[3] were applied (see table 1). The patient characteristics, investigations, treatment and outcome are detailed in table 2.

CASE SERIES

Case 1

A 16-year-old female received her first dose of quadrivalent human papillomavirus (4vHPV) vaccine in her left deltoid muscle. Immediately following immunisation, she experienced numbness at the injection site, which resolved over 15–20 min. She was symptom free until day 4 post-immunisation when she developed numbness and paraesthesia of the left forearm and upper arm. On day 7 post-immunisation, she was admitted to hospital following sudden onset of left arm and leg paralysis associated with upper arm and neck pain. She had multiple normal investigations while an inpatient (see table 2), and was discharged home with physiotherapy and pharmacotherapy management. SAEFVIC clinic follow-up at 2 weeks post-vaccine confirmed resolution of most of her CRPS-1 symptoms except for mild tenderness of the left shoulder and upper arm with a normal neurological examination.

Case 2

A 13-year-old girl received a 4vHPV vaccine (dose 2) in her left deltoid muscle and immediately developed severe left upper and forearm pain, numbness in her left hand, swollen fingers and purplish discolouration of her hand. The hand was also extremely sensitive to touch. She was reviewed by a paediatrician on the following day and given exercises to actively mobilise her arm. Symptoms resolved within 5 days without any further treatment.

Case 3

A 15-year-old girl received her 4vHPV (dose 3) vaccine in her left deltoid muscle and developed

Table 1 Proposed clinical diagnostic criteria for complex regional pain syndrome type 1[3]

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories
   - Sensory: reports of hyperaesthesia and/or allodynia
   - Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
   - Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry
   - 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 at time of evaluation in two or more of the following categories
   - Sensory: evidence of hyperalgesia and/or allodynia
   - Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry
   - Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry
   - Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

pain in her left upper arm within hours of immunisation, which progressed to severe forearm and upper arm pain, numbness and paraesthesia over the next 3 days. Five days post-immunisation she was admitted to hospital for 1 day to maximise CRPS-1 management. Her symptoms persisted over the next 2 months but slowly resolved with simple analgesia, physiotherapy and hydrotherapy.

Case 4

A 12-year-old girl received her third dose of bivalent 2vHPV vaccine in her left deltoid muscle, and 1 h post-immunisation developed paraesthesia in her left fingers and arm, which progressed to left arm weakness over the next few hours. She continued to have distal weakness of the left hand and developed pain in her left forearm and upper arm over the next month. Her symptoms persisted for 7 months post-immunisation with eventual recovery of normal function with supportive management.

Case 5

A 15-year-old male received a single dose of diphtheria-tetanus-acellular pertussis (dTap) vaccine in the left deltoid muscle. He had a small localised reaction at the injection site, but 4 days later developed pain in the left arm and difficulty with movement. He was reviewed in the local emergency department and treated with antibiotics for presumed infection. Eight days post-immunisation he consulted a neurologist, had a normal neurological exam, and was prescribed simple analgesia for symptom management. On review at 3 weeks post-immunisation, he remained symptomatic with a tender, slightly dusky left arm and left-sided lymphadenopathy, but again with a normal neurological examination. He was treated with a 10-day course of oral prednisolone (1 mg/kg). One month post-immunisation he was admitted to hospital for further investigation (see table 2) and management of his persistent symptoms in both his left arm and leg. He subsequently has been seen in the pain management unit at The Royal Children's Hospital, and a number of psychosocial stressors identified. A diagnosis of sympathetically mediated pain was made, as he did not fulfil all the CRPS-1 criteria. Two years post-immunisation he continues to experience pain.

Table 2 Complex regional pain syndrome type 1 post-immunisation: patient characteristics, investigations, treatment and outcome

Case	Age (years)	Sex	Vaccine (dose No.)	Co-morbidity	Affected limb	Pain	Sensory disturbances	Vasomotor symptoms	Sudomotor symptoms	Motor symptoms	Investigations (result)	Therapy	Outcome
#1	16	F	4vHPV* (1)	L4/L5 disc prolapse, polycystic ovarian syndrome (PCOS)	Left arm	Yes	Numbness, paraesthesia	Skin temperature↓	No	Paralysis of left arm and leg, absent reflexes left arm, limited range of movement	MRI brachial plexus, brain and spinal cord —normal Nerve conduction studies—normal	Physiotherapy, mobilisation, carbemazepine, amitryptyline	Resolution of symptoms
#2	13	F	4vHPV (2)	Hashimoto thyroiditis	Left arm	Yes	Allodynia, numbness	Dusky discolouration	Oedema	No	Nil	Physiotherapy	Resolution of symptoms
#3	15	F	4vHPV (3)	Infrequent episodic asthma, chronic fatigue syndrome, food allergies	Left arm	Yes	Numbness, paraesthesia, ↓ light touch sensation	Skin temperature↓	No	Pain on movement, weakness of left arm	MRI brain—normal	Physiotherapy, hydrotherapy, simple analgesia, psychology	Resolution of symptoms
#4	12	F	2vHPV† (3)	Headaches	Left arm	Yes	Paraesthesia	Dusky discolouration, skin temperature ↓	Oedema	Weakness of left arm, limited range of movement	MRI brain—normal	Physiotherapy, analgesia, psychology	Resolution of symptoms
#5	15	M	dTap‡ (booster)	Migraine, enuresis	Left arm, left leg	Yes	No	Dusky discolouration	No	Pain on movement	MRI brain—normal EMG—normal Ultrasound (left arm) —normal Hip plain radiograph —normal	Steroids, antibiotics, amitryptyline, gabapentin, opioids, physiotherapy	Ongoing symptoms

*4vHPV—quadrivalent human papillomavirus vaccine (Gardasil—(CSL/Merck)).
†2vHPV—bivalent human papillomavirus vaccine (Cervenix—(GSK)).
‡dTap—diphtheria, tetanus and acellular pertussis (Boostrix—(GSK)). GSK, GlaxoSmithKline.

DISCUSSION

CRPS-1 in children and adolescents is being increasingly recognised, with the characteristics generally comparable with adults with the same syndrome.[4] As in the adult population, there is a female preponderance with the incidence highest around puberty.[4] The lower extremity tends to be more often affected in paediatric CRPS-1, although this was not seen in our case series, presumably as the proposed inciting event was upper limb intramuscular immunisation. The diagnosis of CRPS is based on history and clinical examination findings that fulfil the current diagnostic criteria.[3] Applying these criteria, the clinical and investigation findings in four of the five cases are consistent with the diagnosis of CRPS-1. Case 5 did not meet all the diagnostic criteria, and a diagnosis of sympathetically mediated pain was made following pain specialist review.

Minor trauma is often the inciting event for CRPS-1 in both adult and paediatric populations.[4] Post-immunisation CRPS-1 in the paediatric population has previously been reported following rubella and hepatitis B immunisation.[1 2] In our case series, different vaccine antigens were administered, including two different HPV vaccines which are both non-live vaccines based on virus-like particle technology, with common adverse events associated with the vaccine including local reactions and pain at the injection site.[6] Case 5 received the dTap vaccine, which has previously been associated with diffuse erythema and self-limited limb swelling in the paediatric population, but not CRPS-1.[7] The authors propose that intramuscular immunisation is sufficient painful stimulus to trigger the development of CRPS-1, and that it is the process of a needle penetrating the skin that is the trigger, rather than a particular vaccine antigen or adjuvant being causally related. This hypothesis is supported by reports of CRPS following other needle-based interventions, including venipuncture and intravenous drug administration.[8 9]

Management of CRPS-1 in children tends to be supportive and utilises a multidisciplinary approach combining physiotherapy, psychotherapy and occasionally medication, with the goals of maximising function and reducing pain. This management approach has a favourable prognosis in children, enabling restored function of the affected limb in the majority of cases.[4] Recent evidence suggests that early introduction of physiotherapy and behavioural therapy is associated with complete recovery in almost all children and adolescents diagnosed with CRPS-1. In addition, delay in diagnosis and initiation of treatment is associated with prolonged recovery.[10] All patients in our case series received physical therapy as the mainstay of their treatment, with the addition of simple analgesia if required. In cases 1 and 5, additional therapy with carbamazepine, amitryptyline and gabapentin was also used for a short period of time with variable benefit. With the exception of case 5, the symptoms were self-limited and lasted between 5 days and 7 months with no recurrence of symptoms identified. Although not identified in this case series, it is important to recognise the potential for relapse of CRPS-1 in the paediatric population. The estimated incidence of recurrence is between 20% and 50%.[4 10] Despite this high incidence, children with a relapse of CRPS-1 tend to respond quickly to standard therapy.[4] The development of CRPS-1 was not felt to be a contraindication to future vaccinations, and all patients were encouraged to receive future routine immunisations as required.

In conclusion, this case series of CRPS type 1 in adolescents temporally associated with immunisation reflect a known complex pain response to a painful stimulus. Enhanced awareness of this syndrome and its potential to occur following immunisation in the paediatric population is vital to the prompt and effective management of this condition in children and adolescents.

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Contributors SR collated and analysed the patient data from SAEFVIC reporting of AEFI during the selected time period and compiled the manuscript. GC reviewed the cases selected for inclusion and helped compile the manuscript. RL provided patient data for a case from the UK and assisted with preparation of the manuscript. JPB reviewed included cases and assisted with preparation of the manuscript. NWC conceived the project, collated and analysed the patient data from SAEFIC reporting of AEFI during the selected time period and helped compile the manuscript.

Competing interests All authors have completed the Unified Competing Interest form and declare that NWC and JPB have acted as chief investigators for epidemiological studies sponsored by vaccine manufacturers (CSL) and serological testing (Merck). Industry-sourced honoraria for sitting on advisory boards (NWC), data safety monitoring boards (JPB), lecturing (NWC) and travel expenses for attendance at scientific meetings, are paid directly to an administrative fund held by Murdoch Children's Research Institute. NWC and JPB do not receive any personal payments from vaccine manufacturers. SR, GC and RL have no financial interests that may be relevant to the submitted work.

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Notes