Study of the incidence and presentation of congenital insensitivity to pain in the UK

Protocol

Congenital insensitivity to pain (CIP) is an extremely rare phenotype characterized by the inability to perceive pain (absence of nociception) from birth. Individuals with CIP do not feel pain from any noxious stimuli, including inflammation and heat [Goldberg et al 2007]. CIP does not cause a generalized sensory neuropathy.

Inability to feel pain leads to repeated injuries and prevents normal healing.

Characteristic Findings [Schon et al 2018]

Age-Related

Infants and young children

- Self-mutilating injuries of the fingers (biting off fingertips) and oral cavity such as loss of the tongue tip, injuries to the inside of the teeth/gums, and avulsion of teeth are common.
- Cuts and bruises may be present.
- Burns due to impaired temperature sensation [Cox et al 2006] can occur.
- Occasional osteomyelitis and septic arthritis, and recurrent otitis media are due to selectively reduced immunity to *Staphylococcus aureus* [Shatzky et al 2000].

Note: (1) Affected individuals may be able to differentiate large temperature changes, but are unable to sense if something is too hot or too cold. (2) A significant number of parents of affected children are suspected of physically abusing their child due to the nature of these injuries [a third in our personal series].

Older individuals

- Painless fractures and joint damage frequently occur and usually lead to permanent damage.
- Bony deformities due to past fractures can occur.
    - Charcot joints (neuropathic arthropathy), most commonly of the ankles, hips, and lumbar spine, are almost universal

- Charcot spine may present with progressive deformity or new motor and/or sensory deficits [Wheeler et al 2014, Staudt et al 2018].

Eyes

All affected individuals are at risk for corneal injuries due to absent corneal reflexes.

- Permanent corneal scarring can develop and is best assessed through a slit-lamp examination.

- Emotional tearing, as opposed to pain induced tearing, is likely to be present [Shatzky et al 2000].

Infections

Apparent selectively reduced immunity to *Staphylococcus aureus* has been observed in some affected individuals, leading to recurrent soft tissue infections, abscesses, and osteomyelitis.

Temperature Regulation, Anhidrosis, and Hyperhidrosis

- Some individuals have anhidrosis (lack of sweating), which disturbs thermoregulation and can lead to recurrent episodes of unexplained fever [Indo et al 1996, Indo 2001]

- Marked hyperhidrosis may be seen in those affected individuals who have a heterozygous pathogenic c.2432T>C (p.Leu811Pro) variant in *SCN11A*

- Hyperpyrexia can be fatal if untreated [Shatzky et al 2000].

- Hypothermia can occur in cold conditions.

Development and Intellect

Development and intellect may be normal or delayed/disabled

- Individuals with CIP caused by biallelic pathogenic variants in *SCN9A* and *PRDM12* typically have normal intellect.

- Individuals with CIP caused by biallelic pathogenic variants in *NTRK1* may have a variable degree of intellectual disability (see Table 1).

- Hyperactivity, impulsivity, and attention deficit are common in children with biallelic pathogenic variants in *NTRK1* [Levy Erez et al 2010].

Other

- Chronic anemia of unknown cause was observed in 22/28 Israeli affected individuals with congenital insensitivity to pain and anhidrosis [Shatzky et al 2000].

- A few individuals have some features of neuropathy (but not the pain), although this does not limit activities [Wheeler et al 2014; Author, personal observation].

Establishing the Clinical Diagnosis of Congenital Insensitivity to Pain

There are no consensus clinical diagnostic criteria for CIP. However, a diagnosis requires a supporting medical history of behaviours / injuries and response to injuries, visible proof of lack of nociception in a conscious individual of normal intellectual ability. Diagnosis is more difficult before 3 years and when a child cannot communicate fully. In those with intellectual disability CIP may be more difficult to diagnose clinically.

Inclusion criteria

Patients aged one month to 18 years

Presenting with a history of insensitivity of pain likely to meet the criteria for congenital insensitivity to pain

and

Self mutilation and / or injuries to lips and/ or digits or permanent joint deformity

Exclusion criteria

Patients who have a raised threshold to pain sensation, but which can be explained by a coexisting underlying neurological disorder e.g. autism, confirmed other hereditary/sensory/autonomic neuropathy

No self mutilation or permanent joint deformity

Confirmed diagnosis of other neurological disease not causing congenital insensitivity to pain

Case ascertainment

The British Paediatric Neurology surveillance unit – BPNSU – send a monthly email to all Paediatric Neurologists registered within the UK . This contains a list of notifiable conditions with inclusion and exclusion criteria available on the website.

Paediatric Neurologist clicks on the link and this will inform the British Paediatric Neurology Surveillance Unit that they have a possible case.

The BPNSU will then inform the investigator.

The investigator sends the patient identification form to the Paediatric Neurologist via email:

<u>The form records:</u>

Referrer name, email, address:
Age of the patient
Parent / carer can they speak English? :

Age appropriate assent / consent forms and information sheets would be supplied with a stamped addressed envelope.

Where these have not been returned after six weeks the investigator will e mail the referrer once to check if they have received the paperwork and if they have any specific questions.

When assent / consent forms have been received the investigator will access the system one database and look at the child or young person's GP records. They should be available for the great majority of cases but if not, they will telephone the GP practice and explain that they would like to request a copy of the patient's notes, who would be the best person to contact and how to send the relevant consent forms / information on the study? Should payment be required for copying the patient notes the investigator could transfer funds to a maximum of £50 per patient.

The copy of patient correspondence would either be transferred securely from an nhs.net address to an nhs.net address or alternatively by tracked delivery of an encrypted datastick.

Once the information is received this would be stored on a password protected electronic file on the Cambridge University hospitals secure electronic system.

Each patient would be allocated a unique study number. A simple data base within the NHS firewall with password protection will be kept of patient's study number, year of birth, referring doctor and unique study number, but not NHS number, hospital number, address, full date of birth.

Clinical and gene variant data would be inserted into an BPNSU-CIP Excel

database within the NHS firewall with password protection using the unique study number.

Key information that would be included:

Sex

Yr birth

Age at first presentation

Self-mutilation/injuries

Burns

Orthopaedic complications including osteomyelitis, presence of imaging and surveillance plan

Safeguarding referrals (unfortunately these are inappropriately done in children with CIP)

Ophthalmic complications and surveillance plan

Temperature regulation

Sweating

Developmental progress

Learning ability

Once this data has been recorded from the clinical notes the family may be contacted if the information is either absent or missing.

Information will be gathered from 1/11/2022to 31/05/2026.

Once the full dataset has been acquired the analysis of the documentation will commence.

Data analysis

We will report

1) The sex, median age of presentation and inter quartile range.
2) How many of the children as raw number eg 11/15 as well as percentage were affected by : Self-mutilation injury(ies), Burns, Orthopaedic complications including osteomyelitis, Safeguarding referrals , Ophthalmic complications, Temperature dysregulation, Reduced sweating, Developmental delay and Learning disability (school-aged children only).

3) How many of the children as raw number eg 11/15, as well as percentage, had a documented plan for surveillance of their orthopaedic status (including radiology) and ophthalmic function.

We aim to publish the information we have ascertained in addition to recommendations on early diagnosis, clarifying diagnostic criteria and surveillance recommendations.

References

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