Congenital pain asymbolia and auditory imperception

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Congenital indifference to pain (pain asymbolia) is a rare condition. Since Dearborn in 1931 described the first case, 51 cases have been reported in the English literature. Congenital auditory imperception as an isolated defect is equally uncommon. It is perhaps the least uncommon of the various types of congenital aphasia. We have recently studied a family in which two siblings showed an association of pain asymbolia and auditory imperception—an association that has not been reported in the English literature as far as we know, although Ford and Wilkins (1938) reported stuttering and specific reading disability associated with pain asymbolia. Boyd and Nie (1949) suggested that there is no specific 'underlying defect in pain asymbolia, but that it is rather an aphasia-like disturbance and hence may be related to the congenital aphasia and perhaps be dependent upon lack of established cerebral dominance'. Alajouanine and Lhermitte (1965) believed that the congenital aphasia is characterized by a defect in language elaboration at the origin of which there may or may not be a cerebral lesion. Our findings regarding the association of pain asymbolia and auditory imperception tend to support the view of Boyd and Nie.

CASE REPORTS

CASE 1 B.D. (U.C.H. No. 156097), a 5-year-old boy of Yoruba parentage, was first seen in April 1966. His parents said he did not hear and talk properly. What he said was an unintelligible semblance of normal speech. He understood sign language very well. He would turn to the source or direction of a sound or voice, but appeared not to comprehend spoken words or commands unless backed by appropriate gesticulations. He was however capable of utilizing a limited vocabulary in Yoruba language—thus he could say properly and in appropriate circumstances 'baba', 'mama', 'odabo', 'kabo': Yoruba words for 'father', 'mother', 'bye-bye', and 'welcome'. He rarely cried, but shed tears normally when he did and appeared incapable of being easily hurt, his parents describing him as 'a very strong boy'. He was very prone to ulcers on his feet. His toilet habits were said to be normal. There was no history of excessive or diminished sweating or of measles infection in early childhood. He had suffered from discharge in the right ear for six months. He had been a normal boy socially and showed no trace of psychotic behaviour except that he often reacted violently when angry or annoyed. The mother was well throughout pregnancy and gave no history of rubella, mumps, or measles. Delivery and the developmental history of the propositus were normal.

The propositus is the third child of his mother (who was 25 years old when he was born) (see Fig. 1). A half-sister was similarly affected. His mother and the half-sister's mother are unrelated. There was no family history of left-handedness, skeletal deformities, premature graying of hairs, white forelock, or goitre.

Examination showed a healthy-looking right-handed boy, the height and weight being 96·5 cm and 13·5 kg respectively. The skull was normal in shape and the circumference of the head was 21·5 in. The face was also normal and the eyes were without hypertelorism, blue sclerotics, or epicantic folds. The upper central incisors were peg-shaped, resembling Hutchinson's teeth in congenital syphilis, but he had no other syphilitic stigmata of congenital syphilis. He had numerous scars on his feet and leg, but these were not remarkable in a Yoruba boy, who habitually walked bare-footed. The skin of the axillae showed the presence of sweat.

Neurological examination showed normal sensorium. The fundi, corneal reflexes, and the other functions of the cranial nerves were found to be normal. There was no detectable abnormality in the motor system, the muscles, the gait, and coordination being normal. Tendon and superficial reflexes were normal. In the sensory system light touch was normal. Communication difficulty made temperature sense impossible to test. His reaction to noxious stimuli was, however, odd. He knew when he was being pricked by a pin, for he could tell the difference by gesture between the sharp and blunt ends. He showed no withdrawal response, evasive or preventive motor reactions, and no facial expression of pain to pin-prick venepuncture, intense pressure on the achilles tendon, or to his skin being transfixed with a needle—which he seemed to enjoy very much. He invited the examiner to repeat the tests while he remained all smiles. There was no alteration in the pulse, blood pressure, respiratory rate, and pupillary sizes to noxious stimuli.

The speech was abnormal. He undoubtedly heard voices but did not appreciate the symbolic significance of most spoken words. Separated from a source of sound by
complexes
the
blood
paper chromatography
showed into
skull,
content
pressure was normal (110 mm cerebrospinal fluid).
was
tearing.
Mecholyl
Biopsy
media
Research, 1966). Psychological tests like
the
test
survey
were normal. His
intelligence
he was mentally normal.

Investigations
Haemoglobin was
10-7 g/100 ml.
M.C.H.C. was 32, white blood cell count
was 12,000 cu. mm with normal differential. The haemoglobin
electrophoretic pattern was AC. Thyroid function tests
were normal: plasma bound iodine was 6-8 µg %, red
blood cell uptake of 131triodothyronine was 11-2/100
ml. haematocrit (12-18 % range of normal); plasma
cholesterol was 138%. Total serum protein was 7-6 g %
(sodium albumin was 3-4 g %) with normal electrophoretic
strip. Serum electrolytes and blood urea were normal.
Serological test (Kahn test) for syphilis was negative in
the blood and cerebrospinal fluid; the latter showed a
protein content of 25 mg %, no cells, and the fluid
pressure was normal (110 mm cerebrospinal fluid).
Biopsy of the skin, which was carried out without local
anaesthesia soon after admission into the hospital,
showed normal fine nerve fibres present in the dermis on
histological examination. A section fixed in formol-
sucrose for neurite impregnation with silver showed no
abnormality. Paper chromatography of urine showed no
abnormal aminoacids. Caloric tests showed normal
vestibular function. Otoscopy showed right chronic otitis
media with central perforation. Unfortunately, the child
was too uncooperative for audiometry. Intradermal
Mecholyl (0-1 ml.) produced profuse sweating, and
subcutaneous Mecholyl (3 mg) produced sweating and
tearing. Miosis was produced when Mecholyl was in-
stilled into the conjunctival sacs. Plain radiographs of
chest, skull, and sinuses were normal, as were tomographs
of petrous bone. Cisternal pneumoencephalography
showed no abnormality. Bell stimuli produced K-
complexes and spindles in the electroencephalogram
obtained during barbiturate-induced sleep.
Progress
The patient was in hospital for eight weeks,
during which news got around of the ‘wonder boy’ who
could not feel pain. Subsequently about four weeks after
hospitalization some laboratory technicians surrep-
titiously paid him several visits, transfixing him with pins
and needles and watching with awe how much he enjoyed
it. He appeared however to discover that he was being
regarded as a ‘freak’ and developed the greatest dislike of
pins and needles. He would fly into an uncontrollable
rage and temper tantrums at the slightest exhibition of
a pin or needle, but would allow himself with much plea-
sure to be subjected to other forms of noxious stimuli like
pressure on the tendon achilles and hot water at
75°C.

When seen and re-evaluated in his home eight months
after discharge from the hospital, he showed complete
indifference to pin prick and venepuncture just as during
his first visit to the hospital. His vocabulary had increased,
and his speech was slightly more intelligible.

Case 2 O.D., a half-sister of the boy (Case 1) was 4
years old when she was brought along with him to the
neurology clinic with the same complaints as described
above for the boy. She showed similar abnormal speech
and stoical indifference to pain. Pregnancy and delivery
were normal, and development was normal except for
disturbance of speech and reaction to pain. There was no
history of otitis media. She shed tears normally on the
few occasions she cried. She was the third child of her
mother who was about 28 years old when the propitious
was born (see Fig. 1).

Examination showed a bright-looking right-handed
child with no neurological or physical deficit except in
her reaction to noxious stimuli and in understanding of
spoken words as described above for her half-brother. In
addition, however, she had blue sclerotics. Her blood
pressure was 95/70 mm Hg and pulse rate was 90/min,
with no evidence of postural hypotension. Sweat could be
felt in the axilla, and sweating and tearing were induced
by subcutaneous Mecholyl.

Haematological indices were normal: haemoglobin
was 11-7 g %, packed cell volume was 38 %. M.C.H.C.
was 31, white cell count was 10,000/cu. mm with normal
differential count, and the haemoglobin electrophoretic
pattern was AA. Plasma bound iodine was 4-4 µg/100
ml., red blood cell uptake of 131triodothyronine was
13/100; haematocrit and serum cholesterol was 114 mg/%
Total serum protein was 8-3 g % with a serum albumin
of 3-6 g % and normal electrophoretic strip. Histology of
skin sections showed normal fine nerve endings. Plain
radiographs of skull, sinuses, and chest, and tomograms
of the petrous temporal bone revealed no abnormality.
Paper chromatography of urine showed no abnormal
aminoacids. Otoscopy showed no abnormality. Caloric
tests for vestibular functions were normal. It is regretted
that the parents did not allow her to be admitted into
hospital for further investigation.

Family Study
The family was visited and examined in the
village where the members lived. Blood was collected
for determination of certain genetic markers: ABO,
MNSs, and Rh groups, haemoglobin electrophoretic
pattern, glucose 6 phosphate dehydrogenase (G-6-P-D),
**FAMILY STUDY**

**Generation I**

Clinically normal  
Age: 70 years  
Not seen

**Generation II**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>M</th>
<th>ABO</th>
<th>Rhesus</th>
<th>MNSS</th>
<th>Haemoglobin</th>
<th>6PGD</th>
<th>Clin. exam.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>/O</td>
<td>cDe/cDE or cDe/cDE</td>
<td>Ms/Ns</td>
<td>B^A/B^C</td>
<td>Gd^A/Gd^B</td>
<td>Normal</td>
</tr>
<tr>
<td>32</td>
<td></td>
<td>A/A</td>
<td>cDe/cde</td>
<td>Ms/Ns</td>
<td>B^A/B^C</td>
<td>Gd^A/Gd^B</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Generation III**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>M</th>
<th>ABO</th>
<th>Rhesus</th>
<th>MNSS</th>
<th>Haemoglobin</th>
<th>6PGD</th>
<th>Clin. exam.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td>A/O</td>
<td>cDe/cdE or cDe/cdE</td>
<td>Ms/Ns</td>
<td>B^A/B^C</td>
<td>Gd^B</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>O/O</td>
<td>cDe/cde</td>
<td>Ms/Ns</td>
<td>B^A/B^C</td>
<td>Gd^B</td>
<td>Normal</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>A/O</td>
<td>(not seen)</td>
<td>Ms/Ns</td>
<td>B^A/B^C</td>
<td>Gd^B</td>
<td>Normal</td>
</tr>
</tbody>
</table>

* Probable because of three children group A could be A/O  

Absent knee and ankle jerks

**DISCUSSION**

There have been several reviews of the literature on pain asymbolia or congenital indifference to pain (Ford and Wilkins, 1938; Critchley, 1956; Fanconi and Ferrazzini, 1957; Ogden, Robert, and Car-
the clinical syndrome. The diagnosis of congenital indifference to pain should be made only in the absence of demonstrable lesion in the peripheral nerves, spinal cord, thalamus, and the cerebral cortex. Exhaustive post-mortem studies in two cases showed no significant evidence of any structural lesion in the central nervous system except for an equivocal diminution in the number of myelinated fibres in the subcallosal fasciculus in one case. The physiological significance of this is unknown (Magee, 1963; Baxter and Olszewski, 1960). Our cases satisfy the criteria of Ogden et al. (1959). The other conditions that may simulate congenital indifference to pain, such as congenital sensory neuropathy, hereditary sensory radicular neuropathy, familial sensory neuropathy with anhidrosis, and familial dysautonomia (Pinsky and DiGeorge, 1966) were also excluded. It should be stressed, however, that in congenital indifference to pain, only the affective component of the response to painful stimuli is absent.

It has been suggested that indifference to pain may wax and wane and tend to subside as the patient becomes older, partly because of regression of the disorder and partly because other qualities of sensation and intellectual functions take over as substitutes (Magee et al., 1961). A mentally normal child may learn to recognize those things which are injurious and thereby avoid damage to himself. Our patient, fully capable of learning, objected to being treated as a circus animal by laboratory technicians, especially when confronted with a pin or needle, but showed complete indifference to other forms of noxious stimulation. This suggests that such subsidence or disappearance of congenital indifference to pain is the result of an avoidance reflex to such conditioning stimuli as evoked either demonstrable trauma or disagreeable psychological effects. In the classical pattern of a conditioned reflex that is not reinforced, eight months later, our first patient had lost the avoidance response to pin prick that he acquired during his stay in the hospital. Bony changes, such as fractures, aseptic necrosis, osteomyelitis, and also neuropathic joints reported in the literature, were not seen in our cases (Westlake, 1952; Houwen, 1961; Silverman and Gilden, 1959, Gwinn, Barnes, Tucker, and Johnson, 1966).

The association of pain asymbolia with auditory imperception shown in the present report suggests that the site of the responsible lesion may be cortical or subcortical, involving the projection fibres to the dominant temporal lobe. Brain (1961) localizes pure word deafness to the auditory receptor area in the dominant hemisphere. In explaining the aphasia sometimes resulting from stereotactic operations on the globus pallidus or optic thalamus for the relief of Parkinsonism, Brain (1961) has suggested the possibility that the corpus striatum is more directly concerned in speech through its corticothalamic and thalamo-cortical connexion. Although Schilder and Stengel (1931) described an acquired asymbolia for pain caused by a lesion in the posterior parietal region of the dominant hemisphere, the nature of the defect in congenital indifference to pain is unknown, despite post mortem studies on two cases (Magee, 1963; Baxter and Olszewski, 1960). Swanson, Buchan, and Alvord (1965) report absence of small primary classical pain-temperature neurones in the spinal ganglia, dorsal roots, spinal cord, and medulla oblongata, and at all levels in the spinal cord the absence of Lissauer's tract—the myelinated tract just lateral to the entering posterior root which continues into the superficial dorsal grey horn. But the case they described, familial sensory neuropathy with anhidrosis, is different from congenital indifference to pain.

The neurophysiology of pain has recently been the subject of controversy (Gerard, 1960; Melzack and Wall, 1965). Although Critchley (1956) suggests that congenital indifference to pain may simply lie at one end of a pain spectrum, at the other end of which are patients who are constitutionally hypersensitive to pain, it is still possible that cortical integration of pain may be defective in those who appear stoical to pain. A patient after frontal lobectomy still feels pain, but does not worry so much about it—that is, the Sherringtonian concept of pain as the sensory adjunct of an imperative protective reflex no longer applies to him. Morphine does not raise the threshold of pain receptors to peripheral stimulation but possibly acts at the cortical level: the message comes to the nervous system as before but no longer seems as important as formerly (Gerard, 1960). These suggest that the integrity of the cerebral cortex is necessary for the full appreciation of pain (British Medical Journal, 1961). There is, of course, a tremendous variability in the reaction of a given individual to a given painful stimulus. In the intense emotion of a battle the severely wounded soldier feels little pain, but in the calmer atmosphere of the hospital base he may require large doses of analgesics (Beecher, 1959). Pavlov's dogs, which received electric shocks, burns, or cuts followed consistently by the presentation of food, eventually responded to these stimuli as signals for food and failed to show even the 'tiniest and most subtle signs of pain' (Pavlov, 1928).

On the other hand, a lesion to account for congenital indifference to pain may be molecular or enzymatic, as has been postulated for congenital aphasia (Eisenson, 1963). Becak, Becak, and Schmidt in 1963 reported two siblings with con-
Congenital pain asymbolia and auditory imperception

genital insensitivity to pain who had an unusual substance in their urine and mosaic trisomy for a chromosome in the D (13-15) group. Late development of speech and poor articulation have been described in association with indifference to pain in familial dysautonomia (Riley-Day syndrome), a disorder believed to be due to abnormal metabolism of presor amine precursors (Riley, 1949; Riley, 1957; Dancis and Smith, 1966; Smithells, 1967). This is tenable if the classical concepts of the neurophysio-pathology of pain are rejected. Melzack and Wall (1965) wrote that 'the concept of a pain centre in the brain is totally inadequate for the sequences of behaviour and experience. Indeed the concept is pure fiction unless virtually the whole brain is considered to be the pain centre because the thalamus, the limbic system, the hypothalamus, the brain stem reticular formation, the parietal cortex and the frontal cortex are all implicated in pain perception. Other brain areas are obviously involved in the emotional and motor features of the behaviour sequence. The idea of a terminal centre in the brain which is exclusively responsible for pain sensation and response therefore becomes meaningless.' The pain relieving effect of anterolateral cordotomy and thalamectomy does not mean that these areas carry a specific pain system. The lesions have multiple effects; they reduce the total number of responding neurones, change temporal and spatial relationships among all ascending systems, and affect the descending feedback that controls transmission from peripheral fibres to dorsal horn cells (Sweet, 1959).

The congenital or developmental asaphias are often of a non-organic nature and thought to be due to lag in the maturation of the part of the central nervous system which deals with the span of auditory attention and with language formulation (Sheridan, 1961). They are often associated with cerebral non-dominance, of which there was no evidence in our patients. We were careful to exclude high-tone deafness in these patients as this may mimic congenital auditory imperception very closely (Creak, 1932; Sheridan, 1961). Our patients, as in the cases cited by Allen (1952), could repeat certain simple words. They did not show any feature of childhood schizophrenia, or of infantile autism, two other conditions which may be confused with congenital auditory imperception or any of the various types of congenital asaphias (Sheridan, 1961; Eisenson, 1963). It is hopefully expected that our patients will improve in their acquisition of language—a not uncommon phenomenon in the congenital asaphias (Sheridan, 1961). There are those who regard developmental auditory imperception as psychogenic and who believe that imperception may follow infantile psychosis (Davis, 1957). Others think it arises as a congenital defect (Berg, 1961). We found no evidence of a psychogenic cause in our cases. We could not demonstrate by standard techniques and investigation any structural defect in one of our patients who was fully investigated.

GENETICS The familial incidence of congenital pain asymbolia or indifference to pain has been recorded by Magee et al. (1961), Silverman and Gilden (1959), and Houwen (1961). Pinsky and DiGeorge (1966) reported two siblings with familial sensory neuropathy and anhidrosis. Congenital sensory neuropathy, although sporadic may be transmitted by a dominant mode of inheritance (Ervin and Steinbach, 1960). Gillespie and Perucca (1960) suggested that congenital indifference to pain is probably recessively inherited. The study in respect of possible genetic markers and linkage in the family reported by us is largely negative. The fact that the two affected half-sibs had different mothers leads to the almost inescapable conclusion that they both inherited an abnormal gene from the father. Further, the different sex of the two propositi virtually rules out X-linkage. The pattern of inheritance is difficult to interpret beyond these two points. If the abnormal gene were dominant, it should have given some manifestations in the father; if it were recessive, we would have to make the supplementary assumption that both wives carried it—a very unlikely assumption in view of the great rarity of the condition. The only other alternative possibilities are the so-called 'incomplete penetrance' (of extreme degree since the father was completely unaffected!) or interaction with other gene(s) present in the propositi but not in their father. Linkage data obtained from this family are negative. Pain asymbolia does not appear to be closely linked to MSNs blood groups, since the two propositi inherited Ns from their father, but so did III–I and III–7 who were unaffected. Linkage to 6-P-G-D cannot be scored because there is no polymorphism in this family. Linkage to ABO blood groups and haemoglobin type cannot be scored because the father is homozygous. The Rhesus genes inherited by the propositi cannot be identified without some risk of ambiguity. It can only be assumed that the child III–7 is illegitimate, since neither of the alleged parents has the B gene.

SUMMARY Two Yoruba siblings (a brother and a half-sister) with a rare association of congenital auditory imperception and indifference to pain have been studied and reported. The nature of the defect and the pathophysiology have been discussed with a brief review of the literature.
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