CASE REPORT

Iniencephaly Apertus - A Rare Neural Tube Defect

Abstract

Iniencephaly is a rare congenital malformation of the CNS, affecting the nape of the neck, occipital bone and cervical vertebrae. Sometimes it is associated with encephalocele and in such cases it is called as iniencephaly apertus. We are reporting a case of iniencephaly apertus seen in our institution. It is caused by defective closure of the neural tube at multiple sites. Closure of neural tube requires adequate formation of paraxial mesoderm in the early embryonic stage. Primary paraxial mesodermal insufficiency results in different types of neural tube defects.

Key words: Iniencephaly apertus, Neural tube defect, Multisite closure of neural tube, Paraxial mesodermal insufficiency.

Introduction

Iniencephaly is a rare congenital malformation of the CNS, occurring prior to closure of cephalic neural fold. The defect lies in the mid-cervical and occipital regions. It was first described by Saint Hilare in 1836. Lewis, in 1897 classified it into iniencephaly clausus (no encephalocele) and iniencephaly apertus (encephalocele is present). The malformation affects three regions, namely, the nape of the neck (inion means nape of the neck), the occipital bone and the cervical spine. The neck is generally absent. There is marked lordosis in the cervico-thoracic region resulting in backward tilting of the head, with the face looking upwards. The retroflexed head is fused to the cervico-dorsal spine. The trunk is generally short and deformed, with overcrowding of the ribs. This condition is associated with multiple anomalies affecting the central nervous system and other systems. Diagnosed is based on the classic triad of retroflexion of head on spine (described as the 'star gazing appearance'), large occipital bone defect and spinal rachischisis in cervico-thoracic region. These features can easily be picked up by an USG as early as 12 weeks, enabling early prenatal diagnosis.

Clinical presentation

A 32 year old second gravida was referred to our hospital at 15 weeks of gestation. Ultrasonography showed anomalies in spine and posterior cranium. There was no history of consanguinity or prenatal exposure to radiation, infections or drug intake. She was on regular antenatal folic acid supplementation. There was no history of congenital anomalies in previous pregnancy. The patient had been administered Mifepris-one, and then referred to our hospital. On admission, she was in labour and underwent abortion. The expelled products of conception were studied in detail. On examination, the conceptus was of male sex and was small for age. It presented gross dysmorphic features with a disproportionately large head, which was retroflexed on the cervical spine (Fig. 1). Neck was absent. The skin of the face was connected directly to the anterior chest wall. Similarly, the posterior scalp was directly connected to skin of the back of the thoracic region. Ruptured encephalocele was seen in the occipital region (Fig. 2), and a large bony defect was palpable around its margins. Spine was distorted with significant shortening and lordosis (Fig. 3).

Fig 1: Fetus with iniencephaly: Crown-rump length – 4 cm; Crown-heel length – 7 cm
Placenta weighed 50 gm, and the cut-section was unremarkable. Microscopy showed second trimester chorionic villi and decidual tissue. Focal intervillous fibrin deposition was noted, which was within normal limits (Fig. 5). The umbilical cord was 12 cm long and showed a single umbilical artery on cross section (Fig. 6). The foetus was not opened up for study of viscera as it was too small (crown-rump length was 4 cm).
Radiological study of the expelled conceptus showed short, malformed vertebral column with lordosis in the cervicothoracic region and overcrowding of ribs (Fig.6).

On the basis of the features of diagnostic triad and the presence of encephalocoele, the case was diagnosed as iniencephaly apertus.

**Discussion**

The incidence of iniencephaly varies greatly from 0.1 to 10 in 10,000\(^2\). Only about 250 cases have been reported so far. It is usually fatal, with only eight surviving cases reported. In India, the incidence has been reported as 1 in 60,000\(^2\). Females are more commonly affected. This may be due to incomplete penetrance of the affected gene on the X chromosome, or due to the fact that male fetuses have less chance of survival\(^4\).

Aetio-pathogenesis is not known. Both genetic and environmental factors have been implicated. A small number of cases have been associated with chromosomal anomalies like trisomy 13, trisomy 18 and monosomy X. Methylene tetrahydrofolate reductase (MTHFR) gene polymorphism and hyperhomocysteinemia have been reported in association with this condition. Environmental factors like low socioeconomic status, poor nutrition and lack of folic acid supplementation may increase the risk. Association with certain drugs like sulphonamides, tetracyclines and antitumor agents has also been reported\(^5\).

Iniencephaly occurs due to an insult in the closure of the cranial part of the neural tube. The classical Zipper model for closure of neural tube states that the closure is initiated at the cervical region, which proceeds rostrally and caudally like a “zipper”\(^6\). According to this concept, NTDs can occur only at the cranial or the caudal end of the neural tube. But it fails to explain the NTDs occurring in between the
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two ends (like iniencephaly) or those occurring at multiple sites. In 1993, Van et. al., proposed the theory of multisite closure of neural tube. According to this theory, initiation of closure of the neural tube takes place at five sites, as depicted in Fig. 6. Closure is initiated at site 1 which extends cranially towards site 4 and caudally to the L2 level. This is followed by closure beginning at site 2 which proceeds towards site 3 and site 4 to meet the closure extending from the respective sites. Finally closure begins at site 5 and proceeds towards L2 level. The part of neural tube beyond S2 level is not derived from the neural plate. It is formed by a different process called secondary neurulation.

It gets segmented to form somites which give rise to the vertebrae. The occipital bone is homologous in development to the vertebrae. It develops from three pairs of somites which finally fuse to form a single bone. Defective development of PAM results in defective neural arches and the associated dysraphism of the spine and the occipital bone. The notochord lies ventral to the neural tube and is seen in close association with the PAM. It is also observed that in PAM deficiency the notochord undergoes kinking, resulting in shortening and lordosis of the skull base and the spine. This, along with the defective neural arches in the cervical region causes retroflexion of the head on the dorsal spine. Various anomalies have been reported in association with iniencephaly. Spina bifida and anencephaly were observed in 50% and 42% of the cases respectively. Other CNS malformations like hydrocephalus, microcephaly, holoprosencephaly, vermian agenesis and cerebellar cysts were also reported. Malformations involving other systems like omphalocoele, pulmonary hypoplasia, diaphragmatic hernia, cardiovascular defects, facial dysmorphism and club foot have also been noticed. The conditions like pulmonary hypoplasia, diaphragmatic hernia, omphalocoele, etc. result from deficient space in the thoracic and abdominal cavities due to spinal deformities and crowding of ribs. Polyhydramnios was seen in 75% of the cases. Association with single umbilical artery (SUA) has been reported by several authors.

In view of the high mortality associated with this condition, it is important to make an accurate diagnosis. This condition has to be differentiated from Klippel Fiel Syndrome (KFS), in which the cervical vertebrae are malformed, but there is no retroflexion of the head. This condition is not fatal and can be surgically corrected. In rare surviving cases, the progressive displacement of the brain through the defect at the crano-cervical junction necessitates surgical intervention. Surgical procedures generally include encephalocoele reduction, duraplasty and ventriculoperitoneal shunt. The risk of recurrence for the subsequent pregnancies is 1-5%. Therefore proper genetic counseling is required for the family. Folic acid supplementation for a period of three months prior to conception and in the antenatal period has to be emphasized.
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References
CASE REPORT

Exogenous Ochronosis - A Rare Pigmentary Disease

Abstract

Exogenous ochronosis is a rare disease characterized by speckled and diffuse pigmentation symmetrically over the face, neck, and photo-exposed areas. It is characterized histologically by banana-shaped ochre-colored deposits in the dermis. It occurs following prolonged use of hydroquinone or phenolic compounds containing creams. Here we report a case of 52 year old lady presented with pigmentation of the face, neck and shoulders of 6 years duration. Exogenous ochronosis was confirmed with histopathology and special staining.

Key words: Exogenous ochronosis, Hydroquinone

Introduction

Ochronosis is a rare disease characterized by speckled and diffuse pigmentation symmetrically over the face, neck, and photo-exposed areas. It is characterized histologically by banana-shaped ochre-colored deposits in the dermis. It can present in exogenous or endogenous form1. Exogenous ochronosis is a localised paradoxical hyperpigmentation of the skin due to prolonged use of bleaching creams containing hydroquinone and other phenolic compounds2. It also occurs following use of antimalarial and products containing resorcinol, phenol, mercury or picric acid. Trinitrophenol benzene3.

Case presentation

A 52-year-old lady with dark pigmentation over forehead, nose, cheeks, chin, neck, ears and upper chest for a duration of 6 years gave a history of treatment with fairness creams for about 3 years. She developed asymptomatic brown-coloured pigmentation over the cheeks, gradually involving neck and upper chest. She had stopped the local application 3 years back. Hyperpigmentation continued to persist in spite of treatment with alternative systems of medicine. Colour became dark brown to black. No history of similar pigmentation in any other areas of skin. No h/o any systemic medication. No history suggestive of any joint, eye, renal or any cardiac involvement. There was no history of dark coloured urine. General examination did not show any abnormality. Systemic examination did not reveal any signs to suggest ocular, renal, cardiovascular or any articular involvement. She had multiple dark brown to black macules and patches in a reticulate pattern over both malar areas, cheeks, pinna and helix of the ears. Few lesions were seen over the forehead. No atrophy or any telangiectasia. Rest of skin was normal.

Skin scraping for fungus was negative. Urine, blood and stool examinations were within normal limits. Urine did not show any change in colour on standing in sunlight. Liver function and renal function tests were within normal limits.

Figure 1:
Pigmentation over the ears

Routine skin biopsy was taken with a differential diagnosis of Lichen planus pigmentosus/ Exogenous ochronosis/ Riehl's Melanosis/ Ashy grey dermatosis. Histological examination was showing the normal epidermis. Dermis was showing golden-brown banana shaped pigments in the papillary dermis between collagen bundles and also near blood vessels. A few scattered inflammatory cells were seen. Ten percent hydrogen peroxide decolourization overnight was done to exclude melanin pigment. Special staining with Prussian blue was done to exclude hemosiderin pigment confirming ochronotic pigment. (Fig.3)
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Discussion
Exogenous ochronosis is due to the prolonged use of bleaching agents leading to deposition of melanin-like brownish-black pigment, derived from oxidised product of homogentisic acid in connective tissues & cartilage. Clinically involved skin appear grey-blue due to Tyndall effect. Endogenous ochronosis/ alkaptonuria is an autosomal recessive deficiency of homogentisic acid oxidase. Exogenous ochronosis is an acquired condition. First described by Findlay et al2 due to prolonged use of bleaching agents with hydroquinone (2-4%) & other phenolic compounds & systemic antimalarials.

Figure 2:
Ivory black pigmentation of face

Figure 3
Banana shaped ochre coloured pigment in dermis

Topical hydroquinone inhibit homogentisic acid oxidase in the dermis causing accumulation of homogentisic acid which polymerises to form the ochronotic pigment4. Ochronotic pigment in contrast to melanin is not bleached by 10% H2O2 after 72 hrs. Banana-shaped ochre coloured deposits in papillary dermis within collagen bundles causing homogenisation & swelling of bundles with few inflammatory cells. Exogenous ochronosis can be clinically misdiagnosed with any other facial hyper-pigmentations and further prescription of whitening or depigmenting agents may complicate the situation resulting in a vicious cycle aggravating the hyperpigmentation.

Conclusion
The actual incidence of exogenous ochronosis seems to be quite low in Indian population, despite the common use of such agents, which might be due to under reporting or a general lack of awareness. Exogenous ochronosis may be frequently missed or under reported entity2. Difficult to treat condition but very much preventable since prolonged topical use of 4% & even 2% hydroquinone can lead to exogenous ochronosis and early diagnosis may help to prevent further aggravation of the pigmentation.

References
CASE REPORT

Acute intestinal obstruction due to internal herniation in a fold associated with a congenital malrotation

Abstract
A 20-year-old boy presented with a combination of pre-mesenteric and post mesenteric (paraduodenal) hernia. The causal factors were congenital and the asymptomatic herniation in the paraduodenal fossa remained undetected until another herniation into a pre-mesenteric fold which became obstructed in the early adulthood. It was a case of partial rotation where the proximal half of the small intestine had failed to rotate and was in the paraduodenal position. The rest of the bowel including the large intestine was normally positioned and fixed. The offending fold of peritoneum was divided and the obstructed loop of intestine was released. After the reduction of paraduodenal hernia, duodenojejunal junction could be seen behind the fold which contained superior mesenteric vessels. This was left as such considering the long-term asymptomatic course it followed.

Keywords: Paraduodenal hernia, internal hernia, malrotation, congenital peritoneal folds

Introduction
Causes originating from perinatal period such as bands, anomalies of the intestinal rotation and congenital defects in the mesentery or omentum could predispose to internal herniation in later life as adults and associated with other anomalies such as congenital diaphragmatic hernia, abdominal wall defects, situs inversus and heterotaxia.(1-4) Some of these causes are related to the abnormalities during rotation of midgut loop which starts around the 6th week of intrauterine life of the fetus.(2) Such abnormalities could be due to non-rotation, mixed or reverse rotation. We report here a case of internal herniation of small intestine into a fossa created by a fold going from ileal mesentery on to retroperitoneal tissue in right iliac fossa. Unless associated with strangulation the outcome of such cases is favourable after surgery, though pre-operative diagnosis is often confounded by lack of specific signs and symptoms.(1)

Case report
A 20-year-old male presented with features of intestinal obstruction of 3 days. Abdominal pain was of acute onset and generalised more on right side with no radiation. There were no aggravating/ relieving factors. Pain was associated with multiple episodes vomiting which was non-projectile, bilious but devoid of foul smell. There was no history of food intake from outside. The patient had no other co-morbidities or any similar complaints in the past. He had no history of previous abdominal surgeries or any other significant family/personal history. He was fully conscious, oriented with a heart rate of 72 per minute and a blood pressure of 120/70 mm Hg. He was afebrile with no pallor, icterus, clubbing, generalised lymphadenopathy or pedal edema. Local examination revealed that the abdomen was distended and tense. Diffuse tenderness was present and more in the right iliac fossa as shown in figure 1. There was no rebound tenderness or guarding or rigidity. The bowel sounds were sluggish. Per rectal examination revealed no abnormal findings. Provisional diagnosis made was that of an intestinal obstruction of an obscure aetiology. Except for elevated total count and ESR, routine investigations did not reveal much. Serum amylase was 79 IU and lipase, 66 IU. USG revealed free fluid in perihepatic, perisplenic, paracolic region. There were multiple dilated small bowel loops noted with sluggish peristalsis. Since the patient refused willingness for surgery, he was admitted in SICU and orders of NPO and continuous ryles tube aspiration and IV antibiotics along with intravenous fluids were given. Patient symptomatically improved.

Fig. 1: Location of tenderness and guarding

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But after, 2 days of admission, pain abdomen increased and the heart rate increased to 112 per minute and features of peritonitis became evident per-abdominally. Emergency laparotomy was undertaken and the finding was that of internal herniation of small intestine into fossa created by a fold going from ileal mesentery on to retroperitoneal tissue in right iliac fossa.

This fold was laid open after reducing the hernia. The small intestine which was dusky, turned pink upon reduction of hernia and half an hour of oxygenation. Bands kinking the hepatic flexure, ascending and ileal loops were also cut and laid open. Appendicectomy was done and drain placed.

The entire non-ischemic proximal small bowel was in the para-duodenal retroperitoneal position entering there behind the superior mesenteric vessels. The para-duodenal hernia with a retro-peritonealised cavity could not be laid open as the superior mesenteric artery formed the anterior boundary of this fold. This hernia was asymptomatic and non-obstructive. Ischemia was, however, in the distal part of the small intestine which had herniated under the fold extending from mesentery to the right iliac fossa.

The position of the duodeno-jejunal flexure is on the right side of aorta and the vertebral body. However, because of malrotation etc. the intestinal loops can end up in a fossa.
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Fig 5: After complete division of the fold the part of the distal ileum which was not herniated is seen in pink and without congestion which extends under the ascending colon or the third part of the duodenum. In the present case there were two herniations one which went para-duodenal and the second one into the congenital fold extending from mesentery to the right iliac fossa. The second one proved to be symptomatic rather than the para-duodenal one.

Fig 6: Paraduodenal hernia with the intestinal loops kept to the left

Fig 7: The paraduodenal hernia with the intestinal loops kept to the right

Fig 8: After the reduction of paraduodenal hernia duodeno-jejunal junction could be seen behind the fold which contains superior mesenteric vessels.

The hernias are of three types namely, paraduodenal, transomental and transmesenteric. (7,8) Transmesenteric variety are about 5-10% in frequency and is situated around the DJ flexure/IC junction and could be both congenital or acquired. (9) Transomental type is rarer at < 5 % and occurs through gastro-colic omentum and is often a double omental hernia. (10) By far the commonest will be para-duodenal and make up more than 50% of all cases and are called the “hernia retroperitonealis”. (11) These occur more on the right side than the left and the male female ratio is often 3:1.

Discussion

Acute mid gut volvulus, chronic midgut volvulus, acute obstruction due to Ladd’s band, internal hernias and caecal volvulus are the clinical presentations of the congenital anomalies presenting in later life. Out of this internal hernias account for only a small percentage of small bowel obstruction cases (0.6% to 5.8%) as observed by a series of 500 cases. Herniation of bowel through an abnormal aperture within the peritoneal cavity is a rare entity and frequently a post-operative diagnosis. (6)

Conclusion

When there is no clearcut diagnosis as to the cause of an obvious intestinal obstruction, a cause may be a congenital abnormality even in older children or adults.
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References
CASE REPORT

Semilobar Holoprosencephaly - A Rare Cephalic Disorder

Abstract
Holoprosencephaly (HPE) is a rare cephalic disorder resulting from incomplete or absent cleavage of the forebrain into distinct cerebral hemispheres. It comprises of a spectrum of malformations affecting the forebrain, usually accompanied by facial anomalies. Semilobar HPE includes structural anomalies of intermediate severity. A preterm male baby at 28 weeks of gestation was still born to a 26 year old woman. Prenatal ultrasonography suggested semilobar HPE. On examination, the baby had microcephaly and midline facial defects. Spina bifida occulta and imperforate anus were also present. On dissection of the brain, the cerebral hemispheres were fused across the midline except in the occipital region. Section across the forebrain revealed a monoventricle, fused thalami and absent corpus callosum. The etiology of HPE is heterogenous. Early antenatal diagnosis is crucial, 3D ultrasonography being the investigation of choice. Survival rate and developmental outcome depend on the severity of brain malformation.

Key words: Holoprosencephaly, midline facial anomalies, prosencephalon

Introduction
Cephalic disorders are congenital anomalies resulting from defective development of the rostral end of the neural tube. Holoprosencephaly is a rare cephalic disorder resulting from incomplete or absent division of the prosencephalon or forebrain into distinct cerebral hemispheres, which usually occurs between 18th and 28th day of gestation. The condition was earlier called arhinencephaly as the olfactory tracts were invariably absent. In 1963, De Meyer and Zeman proposed the term ‘holoprosencephalon’ for this condition, strongly suggesting that the prosencephalon remained holistic instead of dividing into two halves.

HPE has been classified by De Meyer in 1964, into three types, i.e., alobar, semilobar and lobar, in the descending order of the severity of condition. Alobar is the most severe form, with the complete absence of interhemispheric division of the cerebral hemispheres, with a single forebrain ventricle (monoventricle). In semilobar there is partial separation of cerebral hemispheres, especially in the posterior part. Lobar type is the mildest form in which most of the cerebral hemispheres are separated, except in the rostral and ventral parts of the hemispheres.

The middle interhemispheric (MIH) variant, also called syntelencephaly, was described later in 1993, by Barkovich and Quin. It is characterized by non-separation of posterior frontal and parietal lobes. The basal parts of the rostral forebrain which were involved in all the three classic subtypes described earlier are completely separated. Another variant called septo-preoptic HPE was described by Hahn et al., in 2010. It is considered as a subtype of lobar HPE, where non-cleavage is confined to septal/preoptic region of the cerebral hemispheres. HPE is associated with a spectrum of mid-facial anomalies, the severity of which corresponds to the underlying brain malformation. Severe deformities include cyclopia (single median eye/fusion of both eyes in a single orbit), ethmocephaly (close set eyes and a proboscis) and cebophageal (closely set eyes and a nose with single nostril). Milder deformities noted in association with HPE are median cleft lip and palate, hypoplastic midface region, hypotelorism and single maxillary incisor.

Here, we describe the case of a still born preterm baby with semilobar HPE.

Clinical presentation
A male preterm baby was still born to a 26 year old woman, G3P1L1A1. The woman was referred from a peripheral hospital to our institution at 28 weeks of gestation with complaint of leaking PV (preterm premature rupture of membranes). Ultrasonography revealed single intrauterine gestation with growth lag, microcephaly, non-visualised anterior inter-hemispheric fissure, rudimentary lateral ventricle, and partial fusion of thalami, all suggestive of semilobar HPE. She went into spontaneous labour and delivered a still born male baby weighing 2100g.

Her obstetric history revealed that her first pregnancy was antenatally uneventful. She gave birth to a male child who was later diagnosed as deaf and dumb. During her sec-
Second pregnancy, the first trimester scan showed multiple congenital malformations, details of which are not available. During her present pregnancy, she had undergone first trimester and anomaly scans which were both reported to be normal. There was no history of maternal diabetes mellitus, gestational diabetes, TORCH infections or drug abuse. But she had been irregular in her antenatal follow-ups.

The father of the child was also deaf and dumb. The family history was otherwise unremarkable.

On examination, the still born baby was cyanosed and had microcephaly. Midline facial dysmorphism (Fig. 1) was noticed with flattened nasal bridge, hypotelorism, single atretic anterior nasal aperture, microstomia and micrognathia (Fig. 2). There was no cleft lip or cleft palate. Lumbosacral region had a tuft of hair in the midline, indicating spina bifida occulta (Fig. 3). Anus was imperforate and was represented by a dimple (Fig. 3).

The brain was removed from the cranial cavity and examined for structural malformations. The entire forebrain was obtained as a single mass with partial lobation in the occipital region. The median longitudinal fissure was present only in the posterior part (Fig. 4). No gyri and sulci were visible on the external aspect of the cerebral mass. Olfactory bulb and tract were absent bilaterally.

Sagittal section across the posterior part of the forebrain (in line with median longitudinal fissure) revealed a single ventricle (Fig. 5). A cyst containing the developing choroid plexus was noted on the right wall of the ventricular cavity. Corpus callosum and septum pellucidum were not seen. Thalamic and hypothalamic regions were fused (Fig. 5), but the degree of fusion could not be assessed as the tissues in this region were too friable. Parieto-occipital and calcarine sulci could be identified. Cerebellum and brain stem appeared normal.

**Discussion**

Holoprosencephaly is the most common developmental anomaly of the forebrain and midface. It occurs in 1:250 pregnancies and 1:16,000 live births. The discrepancy is due to high rate of intrauterine deaths in HPE fetuses. Though the incidence in live births is small, the condition results in substantial mortality and morbidity.
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HPE is characterized by a spectrum of congenital malformations of forebrain. Along with varying degrees of inter-hemispheric fusion, basal ganglia and the diencephalon are also affected in most of the cases. Hypothalamic non-separation is seen in all cases. Caudate nucleus is more commonly involved (96%), compared to the lentiform nucleus (85%), due to its closer proximity to the midline. Thalamic non-cleavage was noted in 67% only. Ironically, non-cleavage of mesencephalon (midbrain) was noted in 27% of cases suffering from this ‘prosencephalic disorder’, necessitating greater insight into the developmental aspects.

The early development of the prosencephalon involves sequential cleavage along three major planes during the fifth and sixth weeks of development. During the fifth week, the optic vesicles and nasal placodes are formed and separated along a horizontal plane; giving rise to visual and olfactory neural and craniofacial structures. At about the 32nd day of gestation, cleavage occurs in sagittal plane giving rise to paired cerebral hemispheres. The olfactory and hypothalamic regions, hippocampus and the amygdala are defined during this stage. This is followed by cleavage in a coronal plane separating the telencephalon from the diencephalon, which forms the thalamus.

The normal development of the neural tube depends on a complex and balanced interplay between dorsalizing and ventralizing signaling molecules. The prechordal plate lies on the ventral aspect of the forebrain and produces the sonic hedgehog (SHH) proteins. These proteins induce the expression of ventral transcription factors which in turn influence the development of the basal parts of the rostral forebrain (the cortex, the striatum and the hypothalamus).

Defective ventral/ basal induction and patterning result in non-cleavage of rostral prosencephalon and forms the embryological basis of classical forms of HPE. Non-cleavage can extend into diencephalon and mesencephalon as well. But the chances and degree of involvement progressively decreases with increasing distance from the rostral pole.

The embryonic processes that underlie the induction and patterning of the forebrain are also involved in the craniofacial development, giving the possible explanation for the association between midline anomalies of the forebrain and the face.

Barkovich AJ and Quint DJ in 1993 postulated that mesenchyme produced by the prechordal plate plays an important role in the induction of the basal forebrain and midface, anterior skull base and anterior part of falx cerebri. Primary mesenchymal insufficiency could lead to arrested cleavage of the forebrain into two distinct cerebral hemispheres, and also result in defective development of midline facial bones.

In the MIH variant of HPE, there is complete separation of basal forebrain, lentiform nucleus and hypothalamus. No significant craniofacial anomalies are noted in this type. Both these strongly suggest that basal forebrain patterning is normal. Defects in the dorsal induction and patterning have been implicated in such cases.

HPE has a complex etiopathogenesis. It is caused by interaction between multiple genetic and environmental factors. Maternal diabetes, gestational or non-gestational, is an established risk factor. Prenatal exposure to teratogens like alcohol, cigarette smoking, retinoic acid, cholesterol lowering agents, antiepileptic drugs and TORCH agents have also been implicated. The teratogens interfere with the SHH pathway, thereby disrupting the normal basal induction of the forebrain.

Chromosomal anomalies have been implicat-
ed in 25% - 40% of cases, trisomy 13 accounting for nearly half of them. About 25% of the cases are seen in association with multiple malformation syndromes with a normal karyotype, like Smith-Lemli-Opitz, Pallister Hall or velo-cardio-facial syndrome2,5. Mutations in several genes have been identified in non-chromosomal, non-syndromic cases of HPE, the most important genes being SHH, ZIC2, SIX3 and TGIF. SHH codes for Sonic Hedgehog signaling pathway and its mutations have been observed in both isolated and familial cases of HPE2. ZIC2 is the second most commonly associated gene and its mutations have been noted in both classical and MIH variant forms. Patients with mutations of ZIC2 do not suffer from craniofacial anomalies even when HPE is very severe, probably due to the predominant dorsal signaling effects of the gene10. The survival rate and neurological outcome depend on the severity of the structural malformation of the brain. Alobar HPE has a survival rate of only 50% by 5 months of age and 20% by one year of age1. Mild to moderate cases survive into childhood and few of them into adolescence as well7. All children with HPE virtually have some developmental disability and neurological problems. Treatment options for surviving patients is mainly symptomatic and supportive6. The recurrence risk of HPE is estimated to be six percent, and is even higher in familial cases. Prenatal diagnosis of brain and facial anomalies can be made by ultrasonography in the first trimester itself. In case of suspicion of some CNS malformation, fetal Magnetic Resonance Imaging (MRI) can be done to characterize the anomaly7. The parents and family members require a proper genetic counseling about pregnancy outcome, survival rate, treatment options and chances of recurrence.

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References
SYSTEMATIC REVIEW

From Efficacy to Effectiveness of Masks for the Prevention of Lead Uptake in Workers Exposed to Environmental Lead – A Review

Abstract
Lead is an element which enters the human body by inhalation and ingestion. Occupational Safety and Health Administration, California (Cal/OSHA) requires that employers reduce high air lead levels (50μg/m³ or higher) in industries. But, the high levels of environmental contamination, often, found in work environments make it highly desirable to use masks and overalls to prevent lead from entering the body. Studies often prove that the straight application of assigned lead protection factors of mask respirators to actual workplace situations may not always be appropriate. This review attempts to synthesize and discuss the best available evidence on the effectiveness of masks, in terms of the interventions aimed at promoting its use, as compared to similar workplace interventions in preventing the absorption and assimilation of lead in adults employed in industries with high lead exposure. On the whole, this review seems to support the impression that if masks are specifically enforced through education then the fall in blood lead seems to be higher than education alone (31.5% for education with mask vs. 15 - 24% for education without mask). In conclusion, however, there is no solid ground on which to recommend masks alone to protect workers against lead exposure. Interventions such as respiratory masks with worker education and, more importantly, respiratory protection with surveillance based on reliable markers need to be tested in controlled conditions to formulate effective recommendations to prevent and limit lead poisoning in high risk industries.

Key words: Mask, Respirator, Lead poisoning.

Introduction
Lead is a universally present element useful to man in many ways. At the same time, exposure to lead is risky for people who are intimately involved in the specific occupations which employ lead in manufacturing and recycling processes. Lead enters the human body by inhalation and ingestion. Organic forms, only, can be absorbed through skin. Usual intake of lead is averaged at 100 to 350 micrograms per day for population through food, water and air. About 95% of the absorbed lead is bound to Red Blood Cells and the rest is deposited throughout the body in hard and soft tissues. Soft tissue lead is dangerous and can cause gastrointestinal, haematopoeitic, nervous and renal toxicity. Colics, constipation, anaemia, intelligence defects, personality changes and interstitial fibrosis of kidneys are potentially some of the manifestations of lead poisoning (“plumbism”) [1]. According to the present knowledge, blood lead concentrations less than 400 micrograms/litre cannot cause neurological toxicity. In women, impairment of erythropoeisis is indicated to happen at 300 micrograms/litre of blood lead. Fatal effects of lead poisoning are chronic renal failure and acute lead encephalopathy. Irreversible effects include severe peripheral neuropathy resulting in permanent paralysis. Several tools now exist to quantify the adverse effects of low level lead-exposure. Biological tests include a) those which determine the presence of lead in blood and urine and b) those which measure the biochemical and haematological toxic effects of lead. Other tests include the WHO recommended Neuro-behavioral Core Test Battery (NCTB), the Autonomic Nervous System Function (ANS) test, Brain Electricity Active Mapping (BEAM) and Nerve Conduction Velocity. Examples of industries where workers may be exposed to lead in potentially toxic doses include: storage battery manufacture, automobile radiator repair, non-ferrous foundries, secondary and
of lead, incineration, bridge painting, and manufacturers of electronic components, mechanical power transmission equipment, pumps and paints[2, 3]. While the risks are worldwide, industrial safety legislation is not adequate in many developing countries and such legislation that exists is poorly enforced compared with the situation in the West as is evidenced by the continuing use of lead-rich paints in countries like India. In developing countries and, at times in developed countries, many individuals work in conditions of high lead exposure like lead acid battery manufacturing or recycling and painting jobs. Inevitably there is pressure to reduce lead exposure in the general population and in working environments, but any legislation must be based on a genuine scientific evaluation of the available evidence[4]. There are many standards of protection for reducing toxicity of lead. Those range from regularly wearing long sleeved shirt and trousers and regularly washing them in the factory premises itself, using the appropriate mask all day long and improved personal hygiene, for example no smoking in the workplace, washing their hands by a detergent before drinking water or having lunch, and taking a bath after the work. Occupational Safety and Health Administration, California (Cal/OSHA) requires that employers reduce high air lead levels (50μg/m³ or higher). But, the high levels of environmental contamination, often, found in work environments make it highly desirable to use masks and overalls to prevent lead from entering the body. Cal/OSHA advocates the use of half-mask air-purifying respirators as these are cheap and easy to take care of. They are claimed to prevent lead poisoning by protecting the wearer from breathing lead-containing dust or smoke (“fume”). These respirators cannot protect against very high levels of lead, but they do provide enough protection for many industrial and construction workers. P-100, R-100, or N-100 respirator filters, often called HEPA filters, are the standard equipment advised to protect against lead. Specifically the use of masks is being addressed in this review in view of the findings from two major studies which evaluated the effective protection factors for lead-acid storage battery manufacturing workers using powered air-purifying respirators. Approximately 90 percent and 95 percent of the effective protection factors and the corrected effective protection factors of these masks, respectively, were equal to or less than the assigned protection factor of 50. For the negative pressure half-mask respirators, approximately 80 percent and 90 percent of the effective protection factors and the corrected effective protection factors, respectively, were equal to or less than the assigned protection factor of 10. Thus is goes to prove that the straight application of assigned protection factors to actual workplace situations may not always be appropriate [5,6]. This review attempts to synthesize and discuss the best available evidence on the effectiveness of masks, in terms of the interventions aimed at promoting its use, as compared to similar workplace interventions in preventing the absorption and assimilation of lead in adults employed in industries with high lead exposure.

Methodology

All published, unpublished and ongoing trials for improving the work place habits specifically the use of various types of masks with or without filters were included in the review. Cluster randomized, quasi-randomised trials and prospective studies were assessed for quality and included since no randomised controlled trials were available. Pure observational studies were not included. Studies reported only in abstract form were included in the ‘studies awaiting assessment’ category and will be included in analyses when published as full reports. Workers of more than 18 years of age working in industries with high lead exposure such as battery manufacturing/recycling, automobile radiator repairing, non-ferrous foundries, secondary smelters and primary lead smelters, incinerator, bridge painting, manufacturing of electronic components, mechanical power transmission equipment, pumps, paints etc were the subjects of interest. Various interventions to improve workplace habits specifically the use of masks were the focal point of the review. Outcome measures considered were level of awareness among the workers after campaigns as defined by the trial authors, levels of lead in blood before and after a period of minimum 6 months of work, changes in zinc protoporphyrin (ZPP) in blood or delta-aminolevulinic acid (delta-ALA) in urine. Reports considered for inclusion were searched in MEDLINE. All published and ongoing studies involving the use of various types of masks with filters, searching on lead poisoning plus either masks, filters, protective
methods and controlled trials or knowledge improvement thereof were identified. The criteria for inclusion of reports required their having data on some indicator of lead status, workers’ occupations and data collection methods[7]. Data were extracted from the sources onto data extraction forms. Subgroup analyses which were planned included (1) Masks with powered air-purifying respirators and half-mask, negative pressure respirators (2) Health Education with or without provision of masks and (3) Biological Monitoring with or without provision of respiratory protection.

Results

The Occupational Safety and Health Administration (OSHA) has advanced engineering controls over administrative controls and protective equipment to reduce exposures to chemicals in the workplace. However, they often do not emphasize on the application of employee training and motivation programs (such as job safety analysis) to reduce exposures to chemicals. To determine the effectiveness of such programs, a pilot project in an alkyl lead production facility was conducted with 35 employees in an effort to reduce exposures to organic and inorganic lead. Results after 12 months showed a 40% reduction in lead-in-urine and a 24% reduction in lead-in-blood, both indicators of total exposure to organic inorganic lead[8]. There was no control group in this study. The second article reviewed originated from the Institute of Occupational Health, University of Brescia, Italy and dealt with effectiveness of a health education programme for lead-exposed workers regarding work practices, personal hygiene, and life habits in 50 workers exposed to inorganic lead employed in seven small factories. The study was performed in 3 phases over one year. Before the program, blood lead levels were measured, and a questionnaire was administered in order to evaluate the baseline knowledge of the workers about lead poisoning and its prevention. The blood lead levels decreased from 38.2 to 32.3 micrograms/dl and the questionnaire scores improved in a highly significant manner (p < 0.001). These results were obtained both in the short (4 months) and in the medium term (1 year)[9]. 105 lead exposed workers in a factory were targeted for change in the health behavior by setting down and implementing a series of measures. Blood lead concentration and rate of cognition on relevant health knowledge were examined before and after intervened measures. The cognition rate rose from 56.6% to 97.3% after training. Lead concentration in blood decreased by 17.7% (t = 4.10, P = 0.000) and delta-ALA in urine decreased by 23.9% (t = 4.248, P = 0.000) 12 months after intervention. The prevalence of occupational lead absorption and poisoning also decreased. The number of workers with blood lead content > 2.41 mumol/L was decreased from 6 to 3, and > 1.93 mumol/L from 14 to 10 [10]. The prevalence of occupational lead absorption and poisoning also decreased. The number of workers with blood lead content > 2.41 mumol/L was decreased from 6 to 3, and > 1.93 mumol/L from 14 to 10 [10]. Occupational health education as training to all workers (N=31) and managers was provided for reducing the risk of lead poisoning of workers at an assembly section in a battery manufacturing plant in Bangkok, Thailand in 2002. Many workers (80.6-100.0%) noticed and understood the toxicity of lead and the importance of protection against it as an immediate effect of the education programme. In this intervention study, there was a mention of workers having used the appropriate mask all day long as a result of change in attitude towards their work. The average blood lead level of the workers significantly (P=0.002) reduced from 32.7 microg/dl to 22.4 microg/dl, although airborne lead level in the workplace remained unchanged with before conditions[11].

Discussion

It is indeed well-known that certain group of workers employed in occupation such as painting, battery manufacturing, incineration etc. can be exposed to lead in the working atmosphere. Wearing a personal protective device “always” and the interaction with smoking were often found to be significant predictors for blood lead3. These findings have led to lead-safe skills training programmes which aid in learned retention of information about lead exposure; development and retention of positive attitudes toward lead-safe work practices; and development of lasting, positive behavioral intentions to use lead-safe work practice skills and techniques. This review seems to support the impression that if masks are specifically enforced through education then the fall in blood lead seems to be higher than education alone (31.5% for education with mask vs. 15 - 24% for education without mask)[12]. (Table 1)
Table 1
The studies included in the review

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Setting</th>
<th>Mask Type of Study</th>
<th>Number</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee training and motivation programmes such as job safety analysis</td>
<td>Alkyl lead factory</td>
<td>-</td>
<td>35</td>
<td>12 months</td>
<td>24% reduction in blood lead and 40% reduction in lead-in-urine</td>
</tr>
<tr>
<td>Health education on work practices, personal hygiene and life habits</td>
<td>7 small factories</td>
<td>-</td>
<td>50</td>
<td>12 months</td>
<td>Blood lead from 38.2 – 32.3 μg/dl (15.4% reduction)</td>
</tr>
<tr>
<td>Targeted behavioural change programme</td>
<td>Lead exposed workers</td>
<td>-</td>
<td>105</td>
<td>12 months</td>
<td>Lead concentration in blood decreased by 17.7%</td>
</tr>
<tr>
<td>Occupational health education</td>
<td>Battery manufacturing plant</td>
<td>Used</td>
<td>31</td>
<td>-</td>
<td>Average blood lead level from 32.7 μg/dl to 22.4 μg/dl (31.5% reduction)</td>
</tr>
</tbody>
</table>

On the next level of services, lead-surveillance programmes have been conducted in a prospective fashion among workers in several industries. The lead-exposed workers registered significant decreases in blood lead levels if surveillance was combined with control measures. In many developing countries where environmental control measures cannot be effectively and rapidly introduced to protect lead workers, biological monitoring could be a way of identifying and lowering excess lead absorption. However, in developing countries, surveillance may evoke fear of loss of job as substantiated by a study from Singapore where in workers exposed to the lead hazard from a factory manufacturing decorative ceramic tiles were subjected to serial blood lead analysis and 12 workers who were found with high lead levels in blood were suspended from further lead exposure[13]. They were educated on the hazards of lead, the importance of good personal hygiene practices and on the use of the appropriate personal protective equipment. One of the suspended workers left the factory and was not available for evaluation. In the remaining, there was an improvement in overall blood lead results in the subsequent months. In contrast, the Connecticut Road Industry Surveillance Project (CRISP), covering 90 bridge projects and approximately 2,000 workers, was instrumental in lowering bridge worker blood lead levels. Two key features of the CRISP model differing from the exiting OSHA standards at the time were a contract-specified lead health protection program and a centralized system of medical monitoring [14]. A more successful example of occupational health services for lead workers in Korea in a period of 10 years was carried out in three phases, firstly, by increasing awareness among workers concerning the hazards of lead exposure, then, by biological monitoring of zinc protoporphyrin (ZPP) along with a respiratory protection program[15, 16]. A computerized health management system of lead workers was developed, blood lead measurement was added for biological monitoring, and engineering controls were introduced in the workplace to lower air lead levels to comply with air lead regulations. Thirdly, bone lead measurement by X-ray fluorescence was introduced to evaluate total body lead burden. During a period of 10 years,
in spite of the air lead levels remaining generally steady and above the permissible exposure level (PEL), there was steady decline in ZPP and blood lead levels.

Conclusions
In conclusion, there is no solid ground on which to recommend masks alone to protect workers against lead exposure. Interventions such as respiratory masks with worker respiratory protection with surveillance based on reliable markers need to be tested in controlled conditions to formulate effective recommendations to prevent and limit lead poisoning in high risk industries.

References
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CASE REPORT

Emergence of a New Clinical Entity in Kerala

Abstract

We are reporting 2 cases of toilet-seat contact dermatitis in children from Kerala. This was a common condition around the world, and re-emerging clinical entity in USA easy to identify and treat. In the past, exposure to wooden toilet seats were associated with the development of an allergic contact dermatitis on the buttocks and posterior thighs. The wooden seats were changed to plastic or acrylic material and the disease disappeared. Here we present 2 cases of toilet-seat dermatitis in children from Kerala. Factors contributing to the development and re-emergence of the disease is discussed.

Key words: contact dermatitis, toilet seat dermatitis

Introduction

We are reporting 2 cases of toilet-seat contact dermatitis from Kerala. This condition was a common condition around the world and was a simple condition to identify and treat. However it seems to be not clearly identified hence result in a delay of treatment. In the past, exposure to wooden toilet seats and associated varnish, lacquers, and paints led to the development of an allergic contact dermatitis on the buttocks and posterior thighs\(^1\). In recent years, most public facilities have changed to plastic seats, resulting in a change in the clinical presentation of toilet-seat dermatitis. Here we present 2 cases of toilet-seat dermatitis in children from Kerala. It seems that toilet-seat dermatitis is a less identified problem and often may be misdiagnosed as fungal infection or contact dermatitis of undergarments etc. Toilet seat dermatitis should be considered in any child with a dermatitis that involves the buttocks and posterior thighs.

Case presentations

Case No. 1

A 3 year old girl was presented with an itchy eruption over posterior thighs of 3 months duration. She was treated by a paediatrician with antifungal preparations for the last one month without much improvement. No personal or family history of atopy or any other familial disease.

Local examination revealed a crusted lesion over the posterior aspect of the buttocks and back of the upper thigh giving an oval pattern mimicking the shape of the toilet seat without any involvement of the natal cleft and central part of the buttock and gluteal fold. Fungal scraping was negative. Patch test could not be done being a small kid. The child was treated with emollients and topical steroids and was advised to avoid western toilet. The rash subsided within 2 weeks.

Case No. 2

A 10 year old boy was presented with intensely pruritic rash over the buttocks for 3 months duration. There was no history of any local application over the area.
He had the habit of spending about 30 to 40 minutes sitting in the toilet daily playing in water. Till recently he was using a potty and now using water closet of their new house. No history of atopy or any other significant disease was available in the family. Physical examination did not reveal any other abnormality except the crusted and eczematous lesions over the upper half of the buttocks and posterior thigh below the gluteal fold showing a pattern of the oval shape of the toilet seat. Scraping for fungal filaments were done and was negative. Routine blood and urine examinations were within normal limits. Patch test with standard battery and commonly used toilet cleaning liquids were done. Epoxy resins, BHA and BHT were tested strongly positive and cleaning liquid tested were negative.

Figure 3: Patch test done on the back of the child

Discussion
Toilet Seat dermatitis was first described in 1927 as a distinct category of dermatitis venenata. Early during the 1920s wooden toilet seats were commonly in use and the associated varnish, lacquers and paints led to sensitisation and development of dermatitis in United States. The transition from wooden to plastic toilet seats occurred in the 1980-1990 period which led to dramatic decline in the condition. Recently a re-emergence have been documented worldwide. It drew more attention when lymphomatomoid contact dermatitis to wooden toilet seats was reported as a precursor of Cutaneous T Cell Lymphoma.

In Kerala, the use of western closets (WC) were initially limited to adults and elderly. Recently a change in the life style in Kerala has shown inclusion of WC instead of old traditional Indian type of closets. To add it is also noted that almost all newly built houses have WCs in place of old Indian closets. The squatting type of Indian closets do not allow any of body parts to come in contact with the closet. Use of "plastic potties" for providing toilet training to children, followed by direct transition to adult type western closet might have also contributed to the development of toilet seat dermatitis in Kerala. Only one case was reported from Kerala recently. Due to the comfort children tend to spend more time in the closet leading to prolonged contact with the plastic. The offending allergens may be diverse and varied. The allergy can be to either the plastic itself or to an overlying stain or coating. Irritant reaction from harsh cleansers have also been implicated as a cause to it. Identifying the very specific component of plastic that the person is allergic to is difficult to ascertain. The child in our case was found allergic to epoxy resins, BHA and BHT. These chemicals are shown to be used in the processing of plastics. These polyurethanes are chemicals produced by the reaction of toluene 2,4-diisocyanates and polyethers. They form a component of glues, synthetic fibres, surface coatings and sealants. Goossens et al reported a series of allergic contact dermatitis to polyurethane components. Litinov et al has mentioned that harsh alkaline detergents cause skin irritation as they disturb the body's natural acidic mantle.

In the past contact dermatitis was thought to be rare in children, but later shown that it is more common and that patch testing can help in identifying the allergen. But it does pose unique problems in them as they may not have enough surface area for patch testing identification by testing becomes difficult. In our case, total avoidance of use of western toilets was advised and resulted in complete clearance. There were no recurrences. Sitting in the porcelain bowl may help in alleviating the symptoms. Also the use of paper seat covers help to protect the skin from the offending allergen. Rarely altogether shift to Indian style of closets may be needed. Young children should be supervised each time they use the toilets to ensure adequate compliance and to prevent recurrences.

Conclusion
Toilet seat dermatitis continues to be a common condition in children and adults world
Emergence of a New Clinical Entity in Kerala

wide and is on the rise. A high index of suspicion helps in the diagnosis. It may not be just a contact dermatitis always, but can even be a precursor of cutaneous lymphoma. So every patient need to be thoroughly examined and fully evaluated as to the cause of dermatitis.

References