Anonychia Due to Prenatal Phenytoin Exposure

Sir

A
n eight year old girl presented with absence of nails in all fingers and toes except right thumb and left index finger which had rudimentary nails since birth (Figures 1 and 2). She was the only issue born to non-consanguineous parents. Maternal age was 28 years at the time of conception. Mother was a known epileptic and was on phenytoin from the age of 17 years. Drug was taken throughout pregnancy and the drug levels were not monitored. No other family member had absent or hypoplastic nails. Apart from absent nails, patient had minor facial dysmorphic features viz., long philtrum, hypertelorism and low set ear (Figure 3). Her intelligence was normal. There was no history of jitteriness or convulsions during neonatal period or early infancy. There were no other major congenital anomalies. Radiographs of the fingers and toes did not show hypoplasia of distal phalanges. A diagnosis of anonychia due to prenatal phenytoin exposure was made. Total anonychia congenita or hyponychia congenita, a rare autosomal dominant disorder in which all the finger nails and toe nails are absent without significant bone anomalies was unlikely as child did not have affected relatives. There are wide variety of congenital or hereditary disorders in which there is total or partial absence of nails. These disorders are usually associated with other major congenital anomalies.

Fetal phenytoin syndrome occurs approximately 7 to 10% of all babies exposed to phenytoin during pregnancy. The features of this disorder include craniofacial abnormalities (hypertelorism, epicanthic folds, broad depressed nasal bridge, long philtrum, low hair line, abnormal ears), prenatal and postnatal growth deficiency, hypoplastic nails of fingers and toes, distal phalangeal hypoplasia and mental retardation. Other findings occasionally associated include cleft lip and cleft palate, cardiac malformations, microcephaly and ocular defects. Absence or hypoplasia of nails is more common than any other congenital anomaly. Nail abnormalities are associated with increased maternal serum phenytoin concentration. Since the teratogenic effect of the drug is dose dependent, it is prudent to monitor drug levels regularly.

References


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Acute Pancreatitis : An Unusual Complication of Dengue Fever

Sir,

Dengue fever, caused by the flavivirus is the most common mosquito born viral infection in tropical and subtropical countries and has become a major public health concern globally

Fig. 1 : Hands showing absence of nails in eight of ten fingers

Fig. 2 : Feet showing absence of nails

Fig. 3 : Face showing minor dysmorphic features
in recent times. The resurgence of dengue has also been observed in India and dengue outbreaks have been reported from different parts of the country. The dengue infections vary in severity, ranging from non-specific influenza like self limiting illness to life threatening dengue hemorrhagic fever and dengue shock syndrome. The increase spread of disease has led to occurrence of more atypical presentations which may be potentially serious and result in increased morbidity and mortality. It is critical that physicians who monitor dengue illnesses, should be aware and alert to these atypical manifestations. Here, we report a case of dengue fever who presented with acute pancreatitis which is very infrequently reported complication of dengue infection.

35 years old female presented in emergency department with history of high grade fever, headache, retro-orbital pain, myalgia, nausea and vomiting for 5 days followed by severe piercing pain in epigastrium that radiated to back. There was no history of chronic illnesses, abdominal surgery, gall stones, alcohol abuse or any drug intake. On examination she was febrile with cold extremities. Her pulse was 126/min, blood pressure 70/50 mmHg and respiratory rate 22/min. She had mild dehydration. Her abdominal examination revealed diffuse tenderness and sluggish bowel sounds. Cardiovascular, respiratory and central nervous system examination were unremarkable. Laboratory investigations showed hemoglobin 11.2gm%, total leucocyte count 3600/cmm, polymorphs 64% and lymphocytes 36%, hematocrit 38% and platelet count 26000/cmm. The biochemical parameters revealed elevation of liver enzymes, AST and ALT 128 and 83 IU/L, blood glucose 186 mg/dl, urea 46mg/dl and creatinine 1.6mg/dl, calcium 7.2 mg/dl, total protein 6.3gm/dl, triglyceride 154mg/dl and albumin 3.2gm/dl. Pancreatic enzyme determination disclosed an amylase level of 906U/L (normal 20-96) and lipase levels 1112U/L (normal 3-43).

Her dengue serology (IgM by ELISA) was found to be positive while viral markers for hepatitis were negative. Abdominal ultrasound revealed bulky pancreas with necrosis suggestive of acute pancreatitis (Figure 1). She was treated conservatively and discharged after 16 days of hospitalization.

Acute pancreatitis is a rare complication of dengue fever that has been reported very infrequently. Setiawan et al conducted a study that included 148 children with dengue hemorrhagic fever and abdominal pain to assess the pancreatic involvement by abdominal ultrasonography. They reported enlarged pancreas and elevation of serum amylase and lipase in 29% of children.

The exact pathogenesis of pancreatic involvement in dengue infection is not known. It may be due to direct viral invasion, secondary to host immune reactivity or the result of hypotension that remains to be established.

Dengue infection can have varied and multisystemic manifestations which might be unrecognized and unreported because of lack of awareness. Acute pancreatitis is an uncommon but life-threatening complication of dengue fever. Early diagnosis and prompt conservative management of dengue related complications is necessary to avoid serious morbidity and mortality.

References


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Increasing Insulin Requirements

Sir,

Over the last 40 years while treating Type 2 (NIDDM) diabetics, I have noted a marked increase in the average daily insulin requirement. This has increased from of the order of 20-60 units daily to a level of 60-140 units daily (unpublished records of the Diabetic Clinic, Postgraduate Department of Medicine, SN Medical College, Agra as well as observations at the Boston Medical Centre, Agra). Individual patients also show the same trend, except when they develop chronic renal failure, when the insulin requirement declines. This is especially surprising considering that this period has witnessed the progressive introduction of ostensibly better insulins which should be less immunogenic: the replacement of bovine and porcine insulins by more highly purified and then monocomponent insulins, humanised porcine insulin, genetically manufactured human insulin, and long acting modifications. Further it is generally believed that cold chains and quality control during manufacture have in fact improved over the past four decades.

Pari passu, I have also noted the need to introduce insulin in NIDDM patients at a younger age. This could be partly due to our recognition of the benefits of early introduction of insulin rather than persisting with higher and higher doses of oral agents. The use of DPP IV inhibitors sometimes can be used to postpone the switch to insulin therapy.

In individual patients failure to rotate injection sites, liver dysfunction, increasing visceral obesity and increased carbohydrate intake can severely cause increased insulin requirements over time, but none of these is likely to be a cause of increased mean insulin requirements in a group of patients, especially with patients naive to insulin therapy.

The introduction of the long acting analog insulins such as glargine and detemir insulin sometimes allows reduction in the total daily insulin requirement, and so also the introduction of
continuous subcutaneous insulin infusion and insulin pumps, but these are relatively costly, and being significantly different molecules/modes of administration comparison with the earlier insulins is no longer strictly comparison of like with like.

At the recent APICON meeting in Kolkata, 2012, I shared notes with several diabetologists and they also have anecdotally confirmed an increase in average insulin requirements, and I would therefore suggest that a formal documentation of average daily total insulin requirements be analysed from clinic data at various centres.

I had earlier in a letter to your esteemed journal called attention to possible pancreatitis chemical/microorganismal factors due to environmental degradation(pollutants/pesticides) as possible factors in India’s Diabetes explosion, and also to the markedly increased frequency of pancreatitis in the general patient population in North India including nondiabetics. It is possible that these or similar factors may be driving the increased insulin requirements observed in NIDDM therapy. Factors increasing Insulin resistance over the last 40 years would also need consideration. HOMA or similar model analysis of patients to document beta ceil dysfunction and insulin resistance in the same patients would be invaluable, if data were available.

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Eight Cases of Bladder Cancer in Pioglitazone users from India
Sir

The peroxisome proliferator activator receptor gamma (PPAR-γ) agonist pioglitazone is commonly used worldwide for the treatment of type 2 diabetes. Recently, there has been some concern regarding the association of this agent with the development of bladder malignancy. A few retrospective studies, principally based on diabetes registries and adverse event reporting systems, have shown a small increase in the incidence of this form of malignancy in patients, particularly males, who are on pioglitazone. These concerns have led to the suspension of marketing of pioglitazone in France and a recommendation to avoid initiating the drug on new patients in Germany. The USFDA has recommended that a warning be added to the drug prescribing information for pioglitazone in order to reflect this new concern. To date, there have been no reports of bladder cancer among pioglitazone users in India. We report here, eight cases of bladder cancer from India in patients with type 2 diabetes on pioglitazone.

Three of the patients were from Chennai, two from Salem and one each from Belgaum, Hyderabad and Mumbai. Seven of the eight patients were males. The patients ranged in age from 43 years to 76 years. They all had type 2 diabetes and were on pioglitazone for periods ranging from two to nine years. The mean dose of pioglitazone ranged from 15 mg to 30 mg per day. While seven patients had transitional cell (urothelial) carcinoma on biopsy, the nature of malignancy was not clear in the eighth patient. Seven patients are presently on follow up with urologist and oncologist, whereas the eighth patient developed metastases to the liver and lungs and expired in November 2011 after several cycles of chemotherapy and two surgeries. The single female patient developed bladder cancer seven years ago while on 30 mg of pioglitazone. She underwent surgery for the same in the U.S. and was declared free of malignancy. Since the link of pioglitazone with bladder cancer was not known at that time, she was continued on pioglitazone even after the surgery. She developed recurrence of haematuria and pain 4 months later and had to undergo repeat surgery and chemotherapy.

This is, to the best of our knowledge, the first report on bladder cancer among pioglitazone users in India and one of the first in a female patient. Although one cannot draw any conclusions of causality from these eight cases, the development of this relatively uncommon malignancy in eight patients who were on this particular drug does raise concern about the long term safety of pioglitazone. It is also of interest to note that these patients were on much lower doses of pioglitazone, compared to those from the U.S. studies. This raises the possibility that this particular adverse effect of pioglitazone may manifest at a lower dose in Indians compared to the western population, probably due to smaller body mass index or differences in ethnic susceptibility. Clinicians should therefore exercise extreme caution in the use of this drug. Patients should be made aware of this potential side effect of pioglitazone and should be allowed to make informed choices regarding its use. Finally, a nationwide pharmacovigilance study appears to be justified to see whether these cases of bladder cancer with pioglitazone use are just sporadic ones, or whether they represent the tip of the iceberg with many more unreported cases.

References

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Per Oral Endoscopic Myotomy for a patient with Achalasia cardia
Sir

Achalasia cardia is a benign but debilitating primary esophageal motility disorder characterized by incomplete lower esophageal sphincter (LES) relaxation, increased pressure at the LES and failure of esophageal peristalsis. The clinical presentation is mainly with dysphagia, regurgitation and chest pain. Per Oral Endoscopic Myotomy (POEM) is a new addition in the treatment armamentarium of achalasia cardia. To the best of our knowledge POEM procedure has not yet been reported from India.

We performed this procedure on a 52 years female. Patient was symptomatic for progressive dysphagia since 12 years.
She was diagnosed as Achalasia cardia based on endoscopic, barium swallow (Figure 1a) and high resolution manometry (HRM) findings. Prior to the procedure resting LES pressure on HRM was 69.8 mmHg. Her Eckardt dysphagia score was 9/12. Pneumatic dilatation was done once without any symptom relief.

She underwent POEM under general anaesthesia. We used a high definition endoscope (Olympus GIF H180) and transparent cap. After instillation of saline underneath mucosa an incision was made along the right anterolateral wall of the esophagus (Figure 2a) 15cms above the GE junction. We used a hybrid knife (electrogenerator, Erbe Vio 300D; Erbe Elektromedizin, Germany) for making this incision. The endoscope was then inserted into the submucosa at the site of incision and a submucosal tunnel was created from the incision till 1 cm beyond GE Junction (Figure 2b). Continuous infiltration of a solution made of 100ml saline mixed with indigocarmine and 1 ml adrenaline was done to separate the mucosa and to detect any small mucosal tear. Hemostasis was achieved with a coag grasper forceps. The tunnelling time was 53 mins. Esophagus lumen was reinspected for any mucosal tear. The endoscope was re-inserted in the tunnel and muscle cutting was started 4 cms below the mucosal incision (Figure 2c). Circular as well as longitudinal muscle of the esophagus were incised very gently to avoid injury to the mediastinal structures till the end of the tunnel. Time required for this was 25 mins. There was a tiny mucosal break which was closed with a standard endoscopic hemoclip. The mucosal incision was finally closed with six endoscopic clips (Figure 2d). The pneumomediastinum and pneumoperitoneum seen on fluoroscopy at the end of procedure was completely reabsorbed within six hours without any intervention. There was no subcutaneous emphysema. We gave her prophylactic antibiotics and continued for 24 hrs. Patient was kept NPO for 24 hours. As she was tolerating liquids on second day without any discomfort we discharged her. A thin barium study after 48 h revealed rapid emptying of the barium and reduced diameter of the esophagus (Figure 1b). The patient was tolerating soft diet a week later.

Discussion

Treatment of achalasia cardia is directed towards forced relaxation or disruption of LES muscles. Currently available therapies to treat this condition include medications for LES relaxation or facilitation of esophageal peristalsis, BOTOX injection, endoscopic balloon dilatation or Heller’s open or laparoscopic myotomy. However, all of these treatment modalities are limited by their adverse effects, frequent recurrences and complications. The concept of endoscopic myotomy was proposed by Ortega et al three decades ago.\(^1\)
Subsequent animal trials of this procedure were conducted by Pasricha et al in 2007. Haruhiro Inoue from Japan introduced the technique of POEM into clinical practice. Following these studies operative safety, excellent short and long term results of this procedure have been recently published.

The POEM procedure offers intact integrity of EGJ without compromising the adequate surgical division of muscles affected by achalasia. Therefore, it has a potential of combining both benefits of minimally invasive endoscopic procedure and likely long term outcomes of surgical myotomy. Early reports of POEM procedure potentially indicate the reduced reflux rate and its safety. In our patient we used ERBE hybrid knife which has water jet for infiltration and automated settings for mucosal incision, submucosal tunnelling and muscle cutting. Others have used a triangular needle knife (TT knife; Olympus).

**Conclusion**

We report the first Indian case of POEM performed in a patient with achalasia cardia. Initial results of this procedure are encouraging. Comparative trials and long term studies are needed to fully evaluate the utility of this exciting procedure.

**References**


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