Hypothesis: Shwachman’s Syndrome of Exocrine Pancreatic Insufficiency May Be Caused by Neonatal Copper Deficiency

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Abstract. Shwachman’s syndrome is, after cystic fibrosis, the most common cause of exocrine pancreatic insufficiency in childhood. The cause of the disorder is not known but we were struck by the fact that the histological appearances of pancreatic atrophy in this condition resemble those seen in experimental copper deficiency, in which the pancreatic acinar damage persists long after the copper deficiency is relieved. Other features of Shwachman’s syndrome include neutropenia, anaemia and abnormalities of the ribs and of the metaphyses of long bones. All these findings have also been reported in children with copper deficiency during the 1st year of life. We suggest that some or all cases of Shwachman’s syndrome are caused by a period of copper deficiency in early infancy.

Introduction

In 1964 Shwachman et al. [1] described 6 children with exocrine pancreatic insufficiency not due to cystic fibrosis. Four of these patients also had unexplained iron-resistant anaemia and all had intermittent or persistent neutropenia and thrombocytopenia. Subsequently ‘Shwachman’s syndrome’ has been described by many authors and appears to be, after cystic fibrosis, the most common cause of pancreatic insufficiency in childhood. Over the years a number of additional clinical features have been found to be associated with the syndrome, including frequent infections, abnormalities of the metaphyses of the long bones, an ichthyotic skin rash, hepatomegaly, cardiomyopathy and developmental retardation [2, 3]. Since the disorder has been described in siblings, an autosomal recessive inheritance has been thought likely. The cause of the disorder, affecting as it does a large number of tissues, is obscure; one suggestion is that a general-
ised disorder of the microtubules and microfilaments might be responsible [2].

We were struck by a remarkable correspondence between the clinical and radiological features of the early stages of Shwachman's syndrome and those of copper deficiency in the 1st year of life. We then noted that in experimental animals copper deficiency causes damage to the pancreatic acinar cells, which persists long after the copper deficiency is relieved [4, 5]. We therefore concluded that at least some cases of Shwachman's syndrome are caused by copper deficiency in early infancy.

Methods

We identified 61 cases of copper deficiency in early childhood in the world literature [6-32]. We compared the findings in these patients with those of 81 reported cases of Shwachman's syndrome [1-3, 33-48]. From this larger group we selected the 38 patients for whom some clinical information relating to the 1st year of life was available [1, 2, 34, 35, 37, 38, 41, 43-47].

Results

Gastrointestinal Symptoms

It is not surprising that almost all the patients with Shwachman's syndrome had diarrhoea during the 1st year of life. However it is interesting that in one large series [2] there were 6 patients in whom the failure to thrive had been noted some months before the onset of the diarrhoea. Unexplained diarrhoea was reported in 6 of 18 of the children with copper deficiency.

'Feeding difficulties' were noted in 10 of 21 patients with the Shwachman's syndrome in one study [2] and 7 of these needed tube feeding. Unexplained vomiting was noted in 8 out of 36 children with copper deficiency.

Surprisingly little information is available on the long-term follow-up of patients with copper deficiency. In only 4 of the reported cases are the clinical findings 1 year after the identification and treatment of copper deficiency recorded. Two children were entirely well [18, 22], in 1 the diagnosis was coeliac disease and the child was well while on a gluten-free diet [27], and in 1 unexplained diarrhoea persisted after treatment, improved to some extent within 3 months but was still an intermittent problem 8 months later [8].

Haematological Abnormalities

Neutropenia, either intermittent or persistent, has long been regarded as one of the most common features of Shwachman's syndrome. In the original series of Shwachman et al. [1] only 2 out of 5 patients had neutropenia at presentation in the 1st year of life: 2 others developed intermittent neutropenia later. Neutrophil counts in the 1st year of life were recorded for 17 of the children with Shwachman's syndrome. Eight had neutropenia on each occasion studied; 2 had intermittent neutropenia and 7 had no neutropenia. Among the patients with copper deficiency, 18 of 42 patients had neutropenia but in 5 of these [7, 16] neutropenia was intermittent.

In the original series of Shwachman et al. [1] all 5 of the children with symptoms in the 1st year of life were anaemic: 3 required transfusions and in the other 2 haemoglobin values of 9.0 and 10.0 g/dl were noted. In no case was a cause found for the anaemia. In the whole group the haemoglobin level in the 1st year of life was known for 15 patients; in
of these the figure was lower than 11.0 g/dl. Fifty of the patients with copper deficiency were anaemic; almost all had been detected as suffering from copper deficiency because of anaemia.

**Skeletal Abnormalities**

Metaphyseal abnormalities as part of the Shwachman syndrome were first noted by Burke et al. [33] in 1967. In that report and many others, the metaphyseal changes were observed in children older than 1 year. Information about the metaphyses of younger children is only available for 6 patients. In 1, the metaphyses were normal [47], in one irregularity and concavity of the metaphyses around the knee and ankle were noted at 6 months [43], in 1 demineralisation without opacity was found [43], in 1 concavity of the distal ulna and some other metaphyses were found at the age of 2 days [44], in 1 metaphyseal flaring was seen [46] and in the 6th child the irregularity of the proximal metaphyses of the femora and humeri were found at 4 months of age [46]. These early changes are quite unlike those seen later in childhood and are similar to the scurvy-like metaphyseal changes which have been reported in 30 cases of copper deficiency at a similar age. It is likely that the early changes are those of copper deficiency while the later abnormalities reflect secondary damage to bone at sites where bone was laid down at the time of copper deficiency.

The anterior parts of the ribs are often abnormal in Shwachman’s syndrome. Of 8 children with radiographs in the 1st year, 6 [2, 43, 46, 47] had abnormalities consisting of a rickets-like expansion, flaring and cupping of the rib ends. These abnormalities became less prominent with age [47] and were seldom seen after the age of 2.5 years.

Similar abnormalities in the anterior ribs are reported in copper deficiency in the 1st year of life [6, 9, 14, 17, 24].

Transverse lines of increased bone density have been noted in 9 of 21 children in one study of Shwachman’s syndrome [2] and may be similar to the dense bands seen in the metaphyses as a long-term sequel to a period of copper deficiency in infancy [7, 8, 17].

Osteoporosis was thought to be present in bone radiographs of several children with Shwachman’s syndrome [2] and in 1 case [43] was present at the age of 4 months. Osteoporosis is often present in children with copper deficiency.

**Discussion**

It seems to us that retrospective study of reported cases of Shwachman’s syndrome provides strong evidence that abnormalities found in the 1st year of life are very similar to those found in infants with copper deficiency at the same age. The pathological findings in the pancreas of children with Shwachman’s syndrome are also similar to those described in experimental copper deficiency in rats. In both disorders acinar cells are destroyed and replaced by fatty tissue and in both conditions the ducts and islets are preserved.

Shwachman’s syndrome has usually been regarded as inherited in an autosomal recessive manner since it has been described in siblings with apparently unaffected parents [1–3, 33, 46]. The maternal, genetic and nutritional factors which contribute to the pathogenesis of copper deficiency in early infancy are still not understood, but it is likely that whatever the cause of the copper deficiency, similar problems can be repeated.
in a 2nd sibling and cause an illusion of recessive inheritance.

A further reason for doubting the view that Shwachman's syndrome has a simple genetic pathogenesis relates to the time of the earliest symptom of pancreatic insufficiency. Frequently this is not manifest at birth but is first detected at between 2 and 6 months of age. In most of these children symptoms suggestive of copper deficiency were noted from, or soon after, birth. For example one of the original patients of Shwachman et al. [1] was severely anaemic, needing a transfusion at 10 weeks of age, but the diarrhoea did not start until the age of 5 months. A similar case, with anaemia at 2 months but no steatorrhoea till 5 months, was described by Bodian et al. [45].

We suggest that Shwachman's syndrome is caused by a period, perhaps brief, of severe copper deficiency in early infancy. This conclusion has several practical consequences. First, a search for low circulating copper and caeruloplasmin levels in early cases might reveal some infants whose serum levels were still low, and in whom it might be possible to limit the long-term damage to the pancreas and the bones with adequate copper therapy. Shwachman's syndrome also has an appreciable mortality, some of which might be preventable. Second, monitoring for pancreatic insufficiency should be included in the late follow-up of patients with known copper deficiency particularly if there is any evidence of failure to thrive. Third, serum copper and caeruloplasmin levels should be checked in any early cases of metaphyseal chondrodys trophy. Fourth, it is likely that in some patients in whom copper deficiency has been attributed to malabsorption, the malabsorption has been the result rather than the cause of copper deficiency.

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