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Case Report

Forensic Pathology and Newborn Screening for Inborn Errors of Metabolism: Implications for the Middle East

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Abstract

We report the postmortem findings of two infants and one child who died in Iraq. In each case, a specific clinical diagnosis was never established and all died at home. None of the cases had undergone newborn screening tests for inherited diseases.

In case 1, a 3-day old neonate died without ever passing meconium. Autopsy revealed complete small intestinal obstruction due to meconium ileus. This was most likely due to cystic fibrosis. In case 2, a 6 month old boy died suddenly and unexpectedly after developing dehydration from vomiting. Autopsy revealed marked hepatomegaly with fatty infiltration that also involved the myocardium and kidney. This was most likely due to Medium Chain Aacyl Co-A dehydrogenase (MCAD) deficiency. In case 3, a 12-year-old boy died after a progressive neurological disorder of childhood. At autopsy, the body showed cachexia and flexion contractions. The brain showed loss of white matter bulk and thinning of the corpus callosum. The major organs showed no abnormalities. Histologic examination revealed only mild spongy change of the white matter. These findings indicate that the child likely had an organic acidemia, most probably phenylketonuria (PKU).

These cases highlight the critical importance of newborn screening for inborn errors of metabolism in Iraq, including laboratory testing for PKU, MCAD deficiency and cystic fibrosis. Such screening can prevent unnecessary morbidity and mortality in infants and children. On this basis, forensic pathologists should advocate for widespread newborn screening in the Middle East.

Keywords: Forensic Science, Forensic Pathology, Newborn Screening, Metabolism, Middle East.

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العلاقة بين علم الأمراض الجنائي وفحص الأخطاء الوراثية للأيض (الاستقلاب) عند حديثي الولادة: الانعكاسات على الشرق الأوسط

المستخلص

تقدم هذه الورقة تقريراً عن موجودات ما بعد الوفاة لثلاثة من الرضع والأطفال الذين لقوا حتفهم في العراق وخضعوا

لتشريح الجثة الشرعي، ولم يكن هناك أي تشخيص سريري محدد في جميع الحالات المدروسة وماتوا جميعاً في المنزل، وكذلك لم تخضع أياً من الحالات لفحوصات كشف الأمراض الوراثية عند حديثي الولادة. في الحالة الأولى؛ توفي الوليد بعمر ثلاثة أيام دون أن يتبرز العقاق، وكشف تشريح الجثة انسداد كامل للأمعاء الدقيقة بسبب الانسداد العقي (meconium ileus)، وكان ذلك على الأرجح بسبب التليف الكيسي. في حالة الثانية؛ توفي طفل بعمر ستة أشهر فجأة وبشكل غير متوقع بعد معاناته من الجفاف نتيجة التقيؤ، وكشف تشريح الجثة تضخم كبد ملحوظ مع ارتشاح دهني، ويشترك في ذلك أيضاً عضلة القلب والكلى، وكان ذلك على الأرجح بسبب عوز السلسلة المتوسطة للانزيم أسيل كو آ ديهايدروجيناز (MCAD). وفي الحالة الثالثة؛ توفي طفل يبلغ من العمر اثني عشر عاما بعد اضطراب عصبي التدريجي من مرحلة الطفولة، ومن خلال تشريح الجثة تبين وجود دنف (cachexia) وتقلصات ثنيّة (flexion contractions)، وأظهر الدماغ فقدان معظم المادة البيضاء وترقق الجسم الثفني، ولم تظهر الأعضاء الرئيسية أي تغيرات ملحوظة، كما كشفت الدراسة النسيجية فقط تغيرات اسفنجية خفيفة للمادة البيضاء، وتشير هذه النتائج على الأرجح بأن الطفل كان يعاني من احمضاض الدم العضوي وعلى الأرجح بيلة الفينيل كيتون (PKU).

تبرز هذه الحالات الأهمية البالغة لفحص الأخطاء الوراثية للأيض (الاستقلاب) عند حديثي الولادة في العراق، بما في ذلك الفحوصات المخبرية لكل من PKU، وعوز MCAD والتليف الكيسي. ومثل هذه الفحوصات يمكن أن تمنع كلاً من الإمراضية والوفيات غير الضرورية عند الرضع والأطفال. وعلى هذا الأساس يجب على الأطباء الشرعيين الدعوة لفحص الأطفال حديثي الولادة على نطاق واسع في منطقة الشرق الأوسط.

الكلمات المفتاحية: علوم الأدلة الجنائية، علم الأمراض الشرعي، حديثي الولادة، الأيض، الانعكاسات، الشرق الأوسط.

1. Introduction

Medicolegal autopsies can provide a variety of types of information to benefit society. The most visible and widely recognized value of the autopsy is as a tool to assist in the administration of justice. For example, the results of an autopsy can be critically important in a murder trial or other legal proceedings. Information from autopsy can also help characterize accidental and suicidal deaths, thereby providing keys to statistical information that can improve public policy aimed at death prevention. However, the autopsy is also often critically important in sudden natural death from a variety of causes. In a specific case, the discovery of the disease that caused death may be relevant to the family or the health care of the family. For example, autopsies can sometimes reveal an inherited condition that causes unexpected death, such as genetically determined cardiomyopathies or channelopathies [1]. Therefore, medicolegal autopsies performed in sudden death cases, particularly in the young, can discover genetic diseases that may predispose to future deaths in the family. This is an important role for the medicolegal autopsy.

In many countries in the Middle East, hospital or clinical autopsies are not frequently performed. However, medicolegal autopsies are conducted as part of the death investigation system [2]. Therefore, medicolegal autopsies become even more important as a source of vital information in health care for families and society at large.

In Iraq, the medicolegal death investigation system is often called upon to conduct autopsies in cases of sudden death. This includes the death of infants and children that occur unexpectedly, but also after protracted illnesses when the child dies at home. Many such cases appear to represent children with progressive illnesses, mostly with the onset in early life and death from cachexia due to profound neurological impairment. Many of these children appear to have inborn errors of metabolism, neurodegenerative disorders, or congenital malformations. However, virtually never is a clinical diagnosis established and medical intervention is little more than supportive therapy and seizure control with medication. In Iraq, many children die under these circumstances each year and undergo medicolegal autopsy. The paucity of clinical diagnoses in these cases is mostly due to the lack of capacity in laboratory testing in Iraq. Specifically, there is no centralized public health laboratory and the hospital laboratories are at variable states of development. In addition, there is no organized sub-speciality for pediatric metabolic disorders.

We report the autopsy findings of unexpected death in two infants and one child in Iraq. In each case, a clinical diagnosis was never established and death occurred at home after relentless deterioration. The implications of the autopsy findings in these cases provide important lessons

for public health policy makers regarding newborn screening for metabolic diseases.

2. Case Report

2.1 Case 1

A 3-day old male neonate was born of elective Caesarean section after a normal pre-natal course. The immediate post-natal period was complicated by jaundice. The neonate never passed meconium. There was vomiting and abdominal distention. Death occurred at home. At autopsy, there was impaction of the terminal ileum by a mucous plug in the lumen with complete small intestinal obstruction. A micro colon was present. Death was attributed to meconium ileus, most likely due to cystic fibrosis (CF).

2.2 Case 2

A 6-month old girl was the product of a normal pregnancy and delivery. She developed a flu-like illness with vomiting over a period of two days. There was dehydration and reduced food intake. Death occurred at home. At autopsy, there was dehydration with sunken eyes. There was marked hepatomegaly with marked fatty change of the liver. Death was thought to be related to a disorder of fatty acid oxidation, likely Medium Chain Acyl Co-A dehydrogenase (MCAD) deficiency; but confirmatory testing was not available.

2.3 Case 3

A 12-year old boy died after progressive neurological deterioration that began shortly after birth. The neurological deficits included quadriparesis with flexion contractures, generalized wasting, aphasia and mental retardation. It was unclear if seizures were present. Death occurred at home. There was no substantive medical intervention beyond supportive therapy. The clinical diagnosis was not established.

At autopsy, the body was that of a cachectic, pre-pubescent boy with flexion contractures of the lower limbs and generalized disuse muscle atrophy. There were no dysmorphic features or other congenital malformations. The internal organs and tissues appeared macroscopically unremarkable. The brain weighted 1340 grams and appeared to have a slightly more complex pattern of gyral development than usual but polymicrogyria was not present. Coronal sections of the cerebral hemisphere revealed symmetrical and generalized loss of white matter bulk. This was associated with hydrocephalus ex vacuo. There was thinning of the corpus callosum. The cerebral cortex and subcortical grey matter were unremarkable. Horizontal sections of the brainstem and cerebellum showed atrophy of the basis pontis. The medulla was unremarkable. The deep cerebellar white matter and the dentate nucleus appeared unremarkable. Histological examination revealed mild spongy change of the deep cerebral white matter. There was no demyelination. No other significant findings were present.

These findings indicate that the underlying disorder in this case was most likely an amino acidopathy or organic acidemia. Indeed, the most likely diagnosis is phenylketonuria, although other inborn errors of metabolism (e.g., organic acidemias) could not be excluded without laboratory testing.

3. Discussion

The cases we reported in this paper are all related to unexpected deaths for treatable conditions. The deaths resulted because the treatable illnesses were not detected in the neonatal period, thus preventing medical intervention to prevent death [3, 4]. In case 1, meconium ileus was most likely related to cystic fibrosis which escaped detection despite the lack of the passage of meconium shortly after birth. In addition, there was no newborn genetic screening for cystic fibrosis. Cystic fibrosis is an autosomal dominant disease related to mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene resulting in dysfunction in chloride ion homeostasis. The result is exocrine pancreatic dysfunction and cystic lung disease (bronchiectasis). In addition, the tenacious mucus plug can obstruct the lumen in utero and lead to neonatal death by bowel obstruction [5-7]. Newborn screening for cystic fibrosis involves genetic testing for the causative mutation in the CFTR gene. If the disease is detected, medical management can be initiated to prevent complications of cystic fibrosis.

In cases 2 and 3, neonate laboratory screening for disorders of fatty acid oxidation and increased phenylala-

nine concentration in blood or urine was not conducted. MCAD is the most common and fatal inherited disorder of fatty acid metabolism [8-12]. Typically, the presentation is sudden death in a child less than 1 year of age after a period of fasting, such as after a mild viral illness, or diarrhea. Newborn screening for MCAD deficiency involves genetic testing for the causative mutations. Alternatively, the disease can be detected by measuring elevated levels of medium chain fatty acids in blood.

Early detection can prevent premature death from acute metabolic derangements such as hypoglycemia. Other disorders of fatty acid oxidation could not be excluded such as: short chain, long chain and very long chain Acyl Co-A dehydrogenase deficiencies and abnormalities involving carnitine, which is required to transfer fatty acids into the inner mitochondrial membrane (e.g., carnitine palmitoyl transferase and translocase deficiencies). However, these disorders are rarer than MCAD.

PKU was the first genetic disorder that underwent newborn screening [13, 14]. Most cases of PKU are caused by mutations in the gene in coding for phenylalanine hydroxylase. Sustained elevation of phenylalanine levels are toxic to the brain, particularly in the white matter. Unless dietary restriction of phenylalanine contained in foods occurs early in life, there will be profound mental retardation and other severe neurological impairment. In many countries with newborn screening programs, cystic fibrosis, MCAD and PKU would be detected, thus providing the opportunity to intervene and provide life-saving or life enhancing treatment [15, 16]. All the children reported in this paper died, in part, due to the lack of newborn screening.

In the Middle East, ongoing research shows the importance of newborn screening to detect inborn errors of metabolism in the Arab world [17-20]. This is due to a high incidence of genetic disorders due to co-sanguinity, and there is a marked prevalence of autosomal disorders as a result. In particular, PKU is a common disease. Other inborn errors of metabolism for considerations in this context include the organic acidemias such as propionic, methylmalonic, and isovaleric aciduria. In addition, tyrosinemia can present similarly to PKU.

In conclusion, we report 3 cases of death in infancy and childhood that most likely could have been avoided if a newborn screening program was available in Iraq. The main value in these reported cases is that it underscores the importance of newborn screening. Newborn screening for congenital illness takes two main forms – physical examination of the neonate for abnormalities and laboratory testing for inborn errors of metabolism (Table-1). We recommend that forensic pathologists advocate for newborn screening in the Middle East. This will also require the development of pediatricians with subspeciality training in metabolic diseases

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Table 1- *Major autopsy findings of the main inborn errors of metabolism in infants and children.*

Disease	Pathological findings
Congenital hypothyroidism	Cretinism; abnormal thyroid gland.
Phenylketonuria and organic academia, including other disorders with the accumulation of small organic molecules	Cachexia and spongy myelinopathy of the white matter, often with demyelination.
Medium chain acyl Co A dehydrogenase (MCAD) deficiency (fatty acid oxidation disorders)	Fatty change of the liver and other parenchymal organs.
Cystic fibrosis	Meconium ileus with micro colon.
Congenital adrenal hyperplasia	Enlarged adrenal glands.

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