J. D. Gilbert,[1] *FRCPA; G. Scott,*[2] *FRCPath; and R. W. Byard,*[1] *M.D.*

Septo-Optic Dysplasia and Unexpected Adult Death—An Autopsy Approach

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ABSTRACT: A 20-year-old woman who suffered from septo-optic dysplasia died unexpectedly following a presumed viral gastroenteritis. Autopsy and neuropathological examination confirmed optic nerve hypoplasia with absence of the septum pellucidum. Marked adrenal gland hypoplasia reflected hypothalamic hypopituitarism. The small and large intestines were dilated and filled with liquid fecal material. This case demonstrates that individuals with septo-optic dysplasia may be at risk of unexpected death at all ages. The complexity of mechanisms of death in rare dysmorphic conditions may be overlooked if relevant clinical information is not available at the time of autopsy and unless specific steps are taken to clearly delineate the underlying features of the condition.

KEYWORDS: forensic science, septo-optic dysplasia, unexpected death, chlorpromazine

Septo-optic dysplasia (de Morsier syndrome) is a rare condition typified by hypoplasia of the optic nerves, absence of the septum pellucidum, and hypothalamic abnormalities. It is associated with mental retardation and developmental delay (1–3). A case of a 20-year-old woman who suffered septo-optic dysplasia is described to demonstrate that unexpected death may occur in this condition after childhood. In addition, possible mechanisms of death are reviewed and an autopsy approach to older victims with dysmorphic features is discussed.

Case Report

A 20-year-old woman who lived in residential care died unexpectedly. Information available at the time of autopsy was of a history of autism, cerebral palsy, and blindness. There were no other previous health problems noted, and the only medication was chlorpromazine, with chloral hydrate for sleeplessness as required.

On the day before death the deceased had complained of lower abdominal pain and had been anorexic. A viral illness was diagnosed by an attending physician. Overnight she was restless but did not demonstrate any specific symptoms of illness. She was found dead in bed in the early morning.

At autopsy the body was that of a young adult white female with minor facial dysmorphism. Her weight was 64 kg and her height was 157 cm. The right eye was absent. The small and large intestines were mildly to moderately dilated and contained watery fluid with fragments of undigested food. The distal colon contained copious amounts of firm stool without evidence of impaction or stercoral ulceration. The adrenal glands were small and histologically demonstrated marked cortical atrophy (Fig. 1). The pituitary gland was not sampled.

Neuropathological examination revealed bilateral optic nerve atrophy with absence of the interventricular septum (Fig. 2). There were also incidental scattered telangiectases in the cortex, uncus, and midbrain. Routine histologic examination of the hypothalamus did not reveal significant neuronal disruption or gliosis as has been reported (4).

Toxicological examination of blood revealed a chlorpromazine level in the high therapeutic range (0.8 mg/L). Microbiological examination of intestinal contents did not show any pathogens. Vitreous electrolyte levels were not performed.

Subsequent review of the clinical record revealed that the right eye had been removed at four months of age for suspected retinoblastoma. Histological examination revealed retinal dysplasia with no malignancy (Fig. 3). Following further neurological and radiological investigations a diagnosis of septo-optic dysplasia had been made. The deceased had been placed in residential care later in her life and had not suffered any other significant illnesses. She did have a history of chronic constipation.

It was thought that death was most likely due to metabolic derangements associated with hypoadrenalism, precipitated by a possible viral gastroenteritis (despite negative virological findings). It is also possible that chlorpromazine may have played a role in the terminal episode.

Discussion

Review of the literature reveals very few reports of sudden death in septo-optic dysplasia; in fact, Brodsky et al. comment that it is "curious" that the risk of premature death has been generally unrecognized (5). Most deaths occur in very early childhood, with only very rare cases being reported in adults (4). For this reason the current case is of interest in confirming that individuals with this condition may be at risk of premature death despite survival into early adulthood.

The manifestations of septo-optic dysplasia are quite variable and in less severely affected cases the diagnosis may not be established until adolescence. The underlying abnormality involves a defect of cerebral midline structures with optic nerve hypoplasia and hypothalamic dysfunction. In more severely affected cases this may result in blindness, short stature, psychomotor retardation, and hormone deficiencies secondary to hypothalamic hypopituitarism (5). While occasional affected individuals may have normal intelligence, most show reduced intellectual capabilities as in the reported case. Children with this disorder may also have problems with ther-

[1] Forensic Science Centre, Adelaide, Australia.
[2] Institute of Medical and Veterinary Science, Adelaide, Australia.
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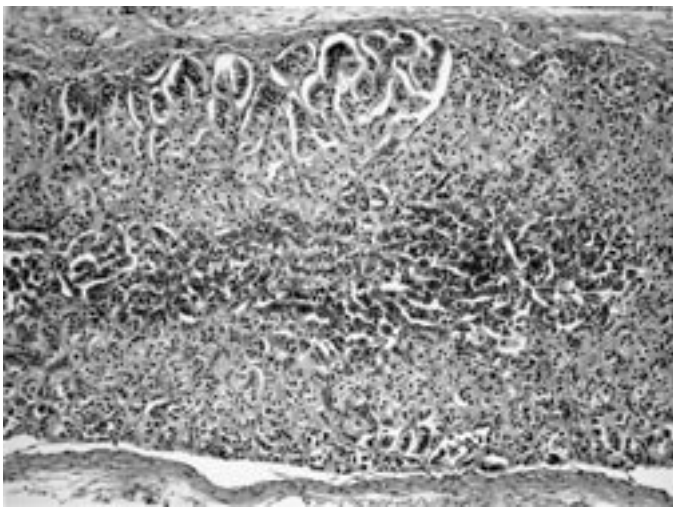

FIG. 1—*Section of adrenal gland demonstrating marked cortical atrophy (Hematoxylin and eosin, X60).*

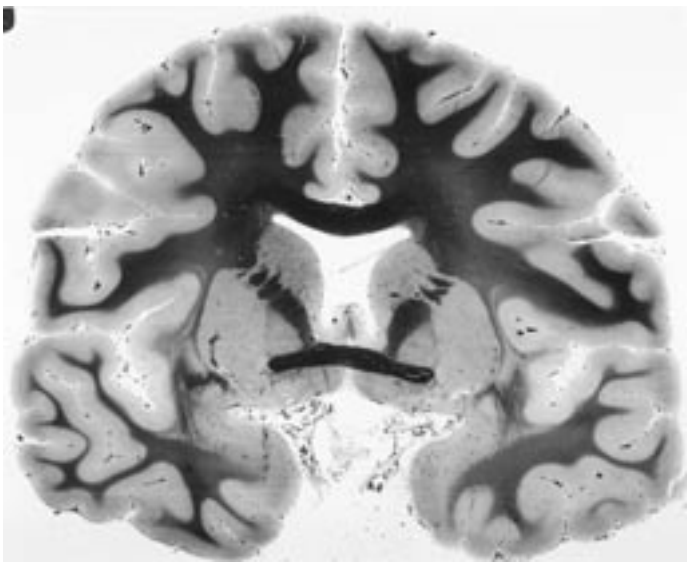

FIG. 2—*Wholemount section of the cerebral hemispheres demonstrating bilateral optic nerve atrophy with absence of the interventricular septum (Weil stain).*

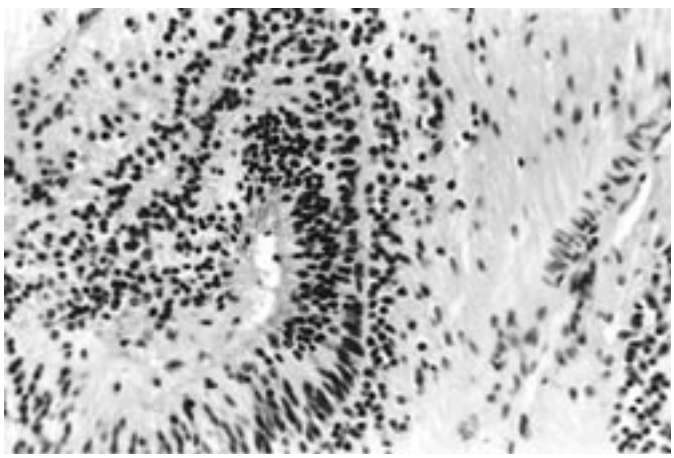

FIG. 3—*Disorganization and folding of the retina characteristic of retinal dysplasia (Hematoxylin and eosin, X200).*

moregulatory control, exhibiting poikilothermia and high fevers of unknown origin with sterile microbiological cultures (6). In addition, affected children may also manifest hypoglycemia secondary to hypocortisolism. Puberty may be normal, delayed, or accelerated (7). The etiology is unknown, with suggestions being made that sporadic cases may be due to environmental teratogens, viral infections, degenerative damage, or to a vascular field defect (4,8). Rare inherited cases may be autosomal recessive and involve mutations in the homeobox gene *HESX1* located on chromosome 3p21.2 (8,9).

The cause of unexpected death in these cases appears to involve a complex interaction between thermoregulatory dysfunction, diabetes insipidus, and corticotrophin deficiency. It is proposed that the additive effects of hypocortisolism, dehydration, high fever, shock, and hypoglycemia may be fatal. It is certainly recognized that children with hypopituitarism are at risk of death from adrenal crisis with hypoglycemia (10). The precipitating factor in fatal cases appears to be viral illness. The features of acute adrenocortical insufficiency include nausea, vomiting, and abdominal pain, with or without fever. Lethargy is followed by somnolence and death, as hypovolemic shock progresses. Acute adrenal insufficiency has been reported following surgery under general anesthesia (11).

Although viral cultures were negative in the reported case, the presence of dilated intestine containing considerable amounts of watery fluid with mucus and fragments of undigested food would be in keeping with an infective gastroenteritis. While the mucosal surfaces were moist, and there did not appear to be any external evidence of dehydration, sequestering of large volumes of fluid within the intestine may have predisposed to an electrolyte disturbance. In addition, chlorpromazine may have had an effect, as adynamic ileus is a reported side effect, and the anti-emetic effects of chlorpromazine may mask certain symptoms and signs of intestinal obstruction. As sudden death has been attributed to phenothiazines due to arrhythmias, convulsions, and hyperpyrexia (12), it is also possible that chlorpromazine may have compounded central nervous system dysfunction in this case.

It is well recognized by forensic pathologists that the assessment of cases of unexpected death may be hindered by lack of clinical information. This has particular significance in individuals who die unexpectedly in institutions who may suffer from a wide range of rare dysmorphic conditions characterized by multiple, subtle malformations, and derangements of homeostatic mechanisms. If the underlying characteristics of a dysmorphic condition are not fully appreciated during the autopsy, there may be a failure to delineate accurately the precise mechanisms of death. This is particularly so if there has been a documented history of epilepsy or aspiration, to which death may be readily and sometimes incorrectly attributed.

Given that a detailed medical history may not be available in cases of chronic syndromic disease, or that the diagnosis may not yet have been established, certain routine steps should be considered. These include the taking of extensive external and internal photographs for later review, skin fibroblasts for cytogenetic and molecular study (or at least snap-freezing material for possible evaluation at later stage), vitreous humor for electrolyte levels, and brain (including the pituitary gland) and spinal cord for formal neuropathological assessment. With the possibility of heritability in some cases and the delineation of specific gene mutations in certain conditions, accuracy of diagnosis and meaningful family counseling may only be possible if appropriate samples have been taken. Where possible, early contact with a medical geneticist or dysmorphologist may also provide extremely useful information on rare conditions, and may enable the linking of a series of apparently disconnected observations into a single syndrome. If this is done at the

time of autopsy, further characteristics of the syndrome can be looked for and any additional tissue samples taken. Careful demonstration of the features of the syndrome in this case at autopsy, with subsequent correlation with antemortem clinical and radiological investigations, enabled clarification of the likely sequence of events in the fatal episode. The possibility of complex drug interactions in rare syndromes should, however, also be considered.

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Additional information and reprint requests:
Professor Roger W. Byard
State Forensic Science Centre
21 Divett Place
Adelaide 5000, Australia
ph: (618) 8226 7700
fax: (618) 8226 7777
email: byardr01@forensic.sa.gov.au