

Syndrome of the month

Cowden syndrome

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Abstract

Cowden syndrome, or the multiple hamartoma syndrome, is a familial cancer syndrome with involvement of various organ systems. Inheritance is autosomal dominant with variable expression. Progressive macrocephaly, scrotal tongue, and mild to moderate mental retardation are important signs indicating the syndrome in young children. Other mucocutaneous symptoms, for example, trichilemmomas in the nasolabial folds and palmar and plantar hyperkeratotic pits, usually become evident later in childhood. They are often accompanied by the appearance of subcutaneous lipomas and cutaneous haemangiomas.

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In 1963 Lloyd and Dennis¹ reported a patient with an apparently new hamartoneoplastic syndrome and proposed the name Cowden disease, referring to the family name of this female. It was not until 1972 that Weary *et al*² documented five new patients with what they called the multiple hamartoma syndrome. As in other hamartoneoplastic syndromes, autosomal dominant inheritance has been shown. Since then, many patients and families with the syndrome have been reported, confirming the autosomal dominant inheritance and inter- and intrafamilial variance.

Clinical features

Patients with the Cowden syndrome may present with one or more of a great variety of clinical signs. Almost pathognomonic are the mucocutaneous lesions, which are usually the least conspicuous. Skin symptoms include acral keratosis and facial trichilemmomas. Oral papillomas or scrotal tongue or both comprise the majority of mucous lesions. Neoplasms of various origins are reported. The danger lies in the development of malignancies (table). Hamartomas, such as lipomas, fibromas, and haemangiomas have frequently been described, but if not actively searched for can often go unnoticed in the patients or their relatives. Benign and malignant tumours include adenoma and follicular cell carcinoma of the thyroid gland, hamartomatous polyps and adenocarcinoma of the digestive tract, fibrocystic breast disease and carcinoma of the breast, and cysts and carcinoma of the female adnexa. The neoplasms often develop at a relatively young age. The most frequently encountered types and incidence of the clinical features are summarised in the table.

Clinical signs and symptoms in young children are often not well documented. Thorough examination can show mucocutaneous lesions, lipomas, fibromas, or haemangiomas at an early age. More important, however, is progressive macrocephaly with mild to moderate delay in psychomotor development, more motor than psychological, as an indicator of the syndrome.^{3,4} Head circumference is normal at birth but in the first year of life macrocephaly becomes progressively evident. Even before the age of 1 year head circumferences are far above the 97th centile for age (fig 1). MRI and CT scans of the skull have proven the macrocephaly to be true and not secondary to hydrocephalus.

In published reports macrocephaly is described in almost one third of patients with Cowden syndrome (table). Not many published data are available to provide information on the incidence of macrocephaly among family members of these patients. Starink *et al*⁵ described a large family of 13 affected members. All but one were macrocephalic. Head circumference in unaffected members was always within the normal range. Recently we have made similar observations in two unrelated families in which all 13 affected members were macrocephalic.^{3,4} In addition to these data, Padberg *et al*,⁶ in 1991, reported two unrelated

Clinical features in Cowden syndrome (n = 98)

Clinical features	Positive/ informative	Percentage
Mucocutaneous	91/98	92.9
Face	81/98	82.7
Mucosa	74/98	75.5
Acral	61/98	62.2
Thyroid	69/98	70.4
Benign neoplasm	61/98	62.2
Malignant neoplasm	7/98	7.1
Gastrointestinal	42/98	42.9
Benign neoplasm	41/98	41.8
Malignant neoplasm	3/98	3.1
Breast*	42/65	64.6
Benign neoplasm*	35/65	53.8
Malignant neoplasm*	12/65	18.5
Lipoma	26/98	26.5
Fibroma	14/98	14.3
(Haem)angioma	33/98	33.7
Reproductive system neoplasm*	29/65	44.6
Macrocephaly	38/98	38.8
Mental retardation	12/98	12.2

* n = 65 (female population).
Adapted from Hanssen *et al*.³

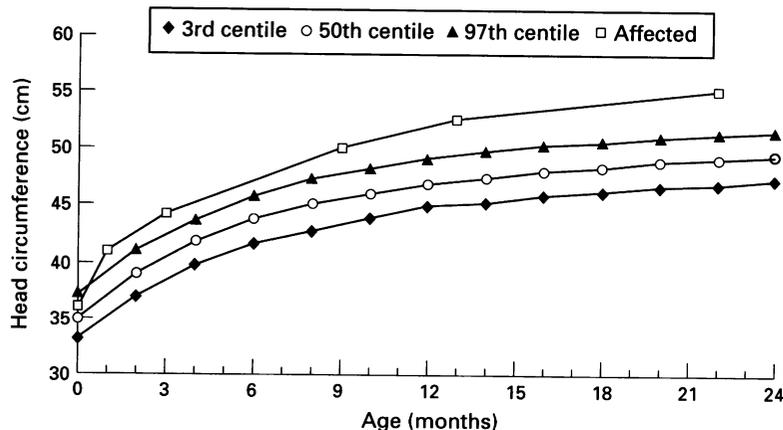


Figure 1 Progressive macrocephaly developing during the first two years of life in a boy with Cowden syndrome.

patients with Cowden syndrome and Lhermitte-Duclos disease. Macrocephaly was said to be present in eight out of nine family members with Cowden syndrome in both families. One macrocephalic child was stated to be mildly mentally retarded but no details were given and not all family members were available for complete investigation.

These data clearly illustrate the importance of macrocephaly as a diagnostic criterion. Progressive macrocephaly may even prove of prognostic value, since in the reported families it appears to coincide with mental impairment in four out of seven patients.

Differential diagnosis

Differential diagnosis between Cowden syndrome, basal cell naevus syndrome, and neurofibromatosis type 1 can be difficult in an individual patient. In these three conditions macrocephaly is progressive in the first years of life, an important clinical difference from other syndromes in which macrocephaly may present from birth onwards, for example, Sotos syndrome and fragile X syndrome. Medical evaluation of family members is necessary in



Figure 2 Cowden syndrome in a mother and son. Note apparent macrocephaly in both.

all cases of unexplained macrocephaly with mental retardation and in all isolated patients with the Cowden syndrome.

Other syndromes such as the Bannayan-Zonana syndrome with macrocephaly, gastrointestinal polyps, and other hamartomatous growths can be distinguished from the Cowden syndrome because of the difference in skin lesions.⁷ It is possible that families or individual subjects reported as isolated true macrocephaly or megalencephaly may in fact be examples of one of these conditions.

Genetics

The Cowden syndrome is inherited as an autosomal dominant trait.² Clinical expression can show great variability. This may not be caused solely by the fact that a great variety of organ systems can be involved. In several families aggravation of clinical signs and symptoms in subsequent generations has been noted. Transmission through affected males resulted in earlier onset of clinical signs and in somewhat more severe expression. Transmission through affected females, however, not only showed earlier expression of the symptoms, but also an undoubtedly much more severe clinical syndrome, even resulting in mental retardation. Carlson *et al*⁸ reported a four generation family with members affected in every generation. Transmission through the female line in this report appeared to result in earlier and more severe clinical expression of signs. Transmission through a male member of the family gave earlier onset of symptoms, but of more or less the same severity. Variable expression in members of the same generation was also noted. Starink *et al*⁵ also reported one family



Figure 3 A 2 year old boy with Cowden syndrome. Note severe macrocephaly.

with affected members in four successive generations. No data were available about the time of onset of the clinical symptoms. Maternal transmission appeared to result in more severe changes in the offspring, whereas paternal transmission resulted in similar or even less severe symptoms. Variable expression was noted in this family as well. In addition to these two large families, there were four informative two generation families. Gentry *et al*⁹ reported two male sibs with possible earlier onset and greater severity of symptoms in the offspring of both. Sogol *et al*¹⁰ described a father with two children, all three of whom had the same time of onset and severity of symptoms. Gorenssek *et al*¹¹ reported a mother with earlier onset of symptoms in her son of 12 years. No conclusions about severity can be drawn at that age. Lloyd and Dennis,¹ in their description of the first patient, mentioned maternal transmission with mental handicap in one of the affected children and normal intelligence in the mother. Recently we have made similar observations in two three generation families.^{3,4}

The findings in the reported families seem to indicate the phenomenon of anticipation. The available data, however, are not sufficient

to draw any definite conclusions. Further investigations will be necessary.

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