

Atypical focal cortical dysplasia in a patient with Cowden syndrome

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ABSTRACT

A macrocephalic girl presented with generalised epilepsy due to focal cortical dysplasia. She later developed multiple hamartomatous lesions and was diagnosed to have Cowden syndrome. The diagnosis was confirmed by identification of a novel frameshift mutation in the *PTEN* gene of the patient.

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Case report

A 10-year-old Chinese girl presented to a paediatric clinic with epilepsy. She had normal intelligence and social interaction ability, and no relevant family history. She had been having recurrent sleep seizures, with generalised twitching of all four limbs, cyanosis, up-rolling of eyeballs, drooling, and urinary incontinence. Her head circumference was 61 cm (5 cm > the 97th percentile). Physical examination was otherwise normal. The electroencephalogram showed an abnormal focus at the right temporo-occipital region. Goldmann perimetry revealed no abnormality. Magnetic resonance imaging (MRI) with contrast showed pachygyria (total loss of sulcation) with hyperplastic white matter and disorganisation of the grey and white matters in the right occipital lobe. A 2.5 cm x 1.8 cm T2 hyperintense area around the right occipital horn was consistent with gliosis. The right occipital lobe was mildly enlarged. Repeated MRI 5 and 7 years after presentation showed no interval changes. Her findings were compatible with focal cortical dysplasia involving the right occipital lobe (Fig 1). The epilepsy was under good control with carbamazepine treatment. She developed a goitre at the age of 16 years, but was euthyroid and ultrasonography showed a multinodular goitre. Hypertrichosis was noted when she was 17 years old. Multiple tiny papules were noted at the perinasal region, of which the patient regarded as coarse skin. At the age of 19 years, she was incidentally found to have iron deficiency anaemia (haemoglobin 96 g/L [reference range, 117–149 g/L], mean corpuscular volume 68.5 fL [82–97 fL], serum iron 2 µmol/L [5.0–30.4 µmol/L], total iron binding capacity 77.1 µmol/L

[44.8–76.0 µmol/L]). She had no gastro-intestinal symptoms, but did receive iron supplements.

She had a left hemithyroidectomy at the age of 22 years for increasing size of a dominant left-sided thyroid nodule that expanded from 1.7 × 1.4 × 0.8 cm to 3.6 × 2.9 × 4.2 cm over 10 months. Fine-needle aspiration showed lymphocytic thyroiditis, and excisional biopsy revealed adenomatous hyperplasia. At the age of 23 years, enlargement of a thyroid nodule in the right thyroid lobe (3 cm in diameter) was noted; fine-needle aspiration suggested it was an adenomatous nodule. Total thyroidectomy was performed, and excisional biopsy revealed an atypical nodule with atypical enlarged vesicular nuclei and small distinct nucleoli. The patient also developed a 3-cm scalp papilloma, shown by excisional biopsy to be fibrous papule. At the age of 24 years, she also experienced coffee ground vomiting; oesophagogastroduodenoscopy showed diffuse glycogen deposits at the lower oesophagus and multiple gastric polyps. Polypectomy yielded lymphoid hyperplasia, and oesophageal mucosa biopsy was reported as showing glycogenic acanthosis.

In view of her multiple benign tumours, the possibility of a hamartomatous polyposis syndrome was suspected. Subsequent clinical examination yielded multiple papillomas over the face and tongue, but there was no pigmentation of the lips. These mucocutaneous features were pathognomonic criteria of Cowden syndrome. Notably, macrocephaly, thyroid adenoma, gastro-intestinal hamartomas (oesophageal glycogenic acanthosis and gastric polyps), and skin fibromas

Cowden綜合症患者的非典型局部腦皮質發育異常

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一名大頭女孩因局部腦皮質發育異常而出現全身性癲癇。她後來出現多個缺陷瘤性病變並透過檢測PTEN基因發現一個新型移碼突變，從而確診Cowden綜合症。



FIG. 1 Magnetic resonance imaging flare sequence showing focal cortical dysplasia at right occipital lobe

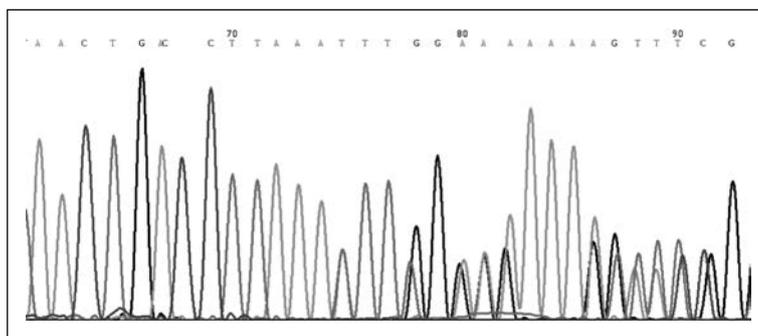


FIG. 2 Mutational analysis for patient with Cowden syndrome
 NM_000314.4(PTEN_v001):c.1023del
 c.1023del in exon 8 of the PTEN gene shown in the anti-sense direction

fulfilled one major and three minor clinical criteria of Cowden syndrome. Mutational analysis of the PTEN gene (Fig 2) showed a heterozygous thymine deletion in exon 8 at position 1023 (NM_000314.4(PTEN_v001):c.1023del). This deletion creates a frame

shift starting at codon Phe341. The new reading frame ends in a stop codon 2 position downstream (NM_000314.4(PTEN_i001):p.(Phe341Leufs*3). This mutation was not detected in the mother. The patient's father was deceased 10 years earlier due to lung cancer, but he did not have macrocephaly or a history of any other tumours.

Discussion

Cowden syndrome was first described by Lloyd and Dennis in 1963.¹ It is characterised by macrocephaly, mucocutaneous lesions, acral (extremity/limb) keratosis, papillomatous papules, and high risk of development of cancer in the breast, thyroid, and endometrium. It is a rare autosomal dominant disease, with an estimated prevalence of 1 in 1 000 000 to 250 000 based on genetic identification.² Lesions can occur in tissues derived from all three embryonic germ cell layers. The subtle and variable clinical manifestations contribute to the difficulty in making a clinical diagnosis. In 1996, the international Cowden Consortium identified germline PTEN (phosphatase and tensin homologue on chromosome 10) mutations as a cause of Cowden syndrome.² This is a tumour suppressor gene encoding a major lipid phosphatase that functions in the phosphoinositide 3-kinase signalling cascade.³ It regulates cellular processes crucial for normal development, including cell proliferation, soma growth, cell death, and cell migration.⁴ The importance on PTEN mutations in making a diagnosis, genetic counselling, and clinical surveillance for the development of malignancies is well recognised. Apart from cancer susceptibility, the PTEN mutation was also implicated as candidate gene in developmental disorder like autism and mental retardation.⁴

Our patient was first suspected to have Cowden syndrome because of the interesting endoscopic findings, as multiple gastric polyps are rarely encountered in young adults. Patients with such polyps should be examined for various genetic syndromes associated with gastro-intestinal polyps, including Peutz-Jeghers syndrome, Cowden syndrome, and Cronkhite-Canada syndrome.⁵ Histology shows *Helicobacter pylori*-negative, non-specific lymphoid hyperplasia. Diffuse oesophageal glycogenic acanthosis has seldom been seen in young adults. The concurrence of oesophageal glycogenic acanthosis and multiple gastric polyps is associated with Cowden syndrome.⁶⁻⁸

Adult-onset Lhermitte-Duclos disease (LDD), which presents clinically with progressive cerebellar sign and increased intracranial pressure, is also a feature. A dysplastic cerebellar gangliocytoma is now considered to be one of the central nervous system (CNS) pathognomonic criteria by the revised Cowden Syndrome Consortium. The other overt CNS manifestations of Cowden syndrome included

macrocephaly, autism, developmental delay, brain tumour, and LDD. The unique feature in our patient was the presentation with generalised epilepsy in childhood and the identification of focal cortical dysplasia in the right occipital region. To our knowledge, such brain MRI imaging has not been described previously in Cowden syndrome.⁹ Apart from regulating cell growth, the *PTEN* gene also plays a role in cell migration. It interacts with focal adhesion kinase, which results in the inhibition of cell migration and spread. Focal cortical dysplasia is a kind of neuronal migration disorder. Our patient was noted to have a right occipital focal cortical dysplasia and right megalencephaly. These features suggest CNS manifestations of the *PTEN* mutation. Inclusion of this feature in Cowden syndrome may facilitate early diagnosis.

Cowden syndrome represents a late-onset phenotype of the *PTEN* mutation. Early presentation of *PTEN* mutations include Bannayan-Riley-Ruvalcaba syndrome and autism spectrum disorder with macrocephaly. Bannayan-Riley-Ruvalcaba syndrome is a congenital disorder characterised by macrocephaly, hamartomatous intestinal polyps, lipomas, and pigmented macules on the penis. To our knowledge, our patient represents a new *PTEN* mutation phenotype, with macrocephaly and focal cortical dysplasia at the occipital region and subsequent full-blown presentation of Cowden syndrome.

In conclusion, we believe we have identified a new phenotype of Cowden syndrome and a new *PTEN* indel mutation. This *PTEN* mutation appears to cause megalencephaly, epilepsy, focal cortical dysplasia in the occipital region in childhood, and multiple hamartomatous lesions in late adolescence and early adulthood. The inclusion of focal cortical dysplasia in the occipital region as a CNS feature of the *PTEN* mutation could facilitate early diagnosis of *PTEN* mutation syndromes, and clinicians to undertake early surveillance for possible malignancies. In the latest published prospective study of the Ohio cohort of patients with germline *PTEN* mutation, the penetrance of breast cancer was found to begin at around the age of 30 years rising to an estimated 85% lifetime risk.¹⁰ The lifetime risk of

breast cancer in females with *PTEN* mutations was even higher than the best estimates for individuals with *BRCA1* or *BRCA2* mutations.¹¹ The *PTEN*-related endometrial cancer risk begins at the age of 25 years rising to 30% by the age of 60 years.¹⁰ The thyroid cancer risk begins at birth and continues lifelong.¹⁰ Risks of colorectal and kidney cancers begin at around the age of 40 years, with a lifetime risk of 9% and 34%, respectively.¹⁰ The earliest reported age of onset of melanoma was in a 3-year-old patient.¹⁰

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