Overgrowth syndromes are a diverse group of rare disorders, each comprising a partially overlapping subset of clinical features. Their severity, natural history and complications vary widely and disfigurement is a common association and therefore correct diagnosis is clinically important. None is straightforward to diagnose and both under- and over-diagnosis may occur. We report a case of an overgrowth syndrome characterized by a novel constellation of physical features that may represent either a delimited case of Proteus syndrome or an as yet uncharacterized overgrowth disorder. The importance of careful clinical examination and history taking is highlighted, as are the challenges of clinical diagnosis in overgrowth disorders.

Case report

A 29-year old lady presented to our hospital, following an episode of severe, left-sided cephalgia associated with transient, left monocular blindness. Persistent distortion of the temporal aspect of her left visual field was noted on formal ophthalmological assessment. Magnetic resonance imaging (MRI) of brain and craniocephalic angiography were normal. She was given a diagnosis of retinal migraine.

Upon examination, a number of physical abnormalities were present. She had focal overgrowth of the radial aspect of her right hand (Figure 1A); surgical amputation of the index finger at the metacarpal-phalangeal joint; a swan neck deformity of the middle finger, fullness and increased girth of the radial aspect of the hand and bowing and soft tissue hypertrophy of the forearm (Figure 1B) and distal upper arm on the same side. The circumference of the right biceps was 4 cm greater than the left.

A 13 cm in diameter firm, smooth, subcutaneous mass was noted over the posterior aspect of her right shoulder. An MRI examination showed increased subcutaneous fat on the right upper arm and lobulated and infiltrating fatty tissue surrounding and intermixed with the deltoid musculature.

A flat melanocytic nevus (clinically junctional nevus) in her groin area and a café-au-lait patch over her left thigh were present. Her physical examination was otherwise unremarkable. There was no evidence of macrocephaly (occipitofrontal circumference was 56 cm).

Her right index finger had been amputated in infancy as its size resembled that of an adult thumb at the time of birth and showed striking, excessive and rapid overgrowth after birth. The thumb had been growing since birth and the forearm was noted to enlarge in length and circumference for 3 years before this admission. New bone growth was noted on radiography (Figure 1C) with bone architecture appearing abnormal and distorted on a series of radiographic images. An MRI confirmed lipomatosis but showed no additional features, specifically no hypertrophy of the median nerve was present.
The patient's medical history was notable for epilepsy in childhood; an excised and histopathologically confirmed fibrolipomatous neural hamartoma (right palm); excised recurrent exostoses affecting the proximal phalanx of the patient's right middle finger; mesenteric adenitis and ruptured ovarian cysts (of unconfirmed histopathology) at the age of 16 years; and primary hyperparathyroidism due to a parathyroid adenoma that was excised when the patient was 26 years old. No other family members were reported to have similar findings.

**Discussion**

The patient presented with focal asymmetrical overgrowth, dysregulated adipose tissue growth and ruptured ovarian cysts, which prompted us to consider a diagnosis of Proteus syndrome. The currently accepted diagnostic criteria for Proteus syndrome require that patients have the three general criteria of mosaic pattern, sporadic (non-familial) occurrence and progressive course, all of which this case meets (Table 1). The criteria also require specific findings, and this patient most closely conforms to criterion b with asymmetric progressive overgrowth of the thumb and she may have had ovarian cystadenomas. Her melanocytic nevus is similar, but not the same as the classic linear epidermal nevus, both of which are pigmented lesions. On this basis, we conclude that this patient presents with features that overlap with, but do not quite meet the criteria for a diagnosis of Proteus syndrome.

Other overgrowth syndromes, such as Hemihyperplasia Multiple Lipomatosis and CLOVE were considered but were thought to be less likely. The former was thought to be unlikely because of the absence of vascular malformations and multiple lipomata and the presence of progressive overgrowth associated with skeletal distortion. CLOVE is unlikely due to the lack of vascular malformations and epidermal nevi.

A disorder of patchy or mosaic overgrowth, Proteus syndrome has been hypothesized to be caused by a somatic mutation. Such a mutation will have occurred late in development and subsequently affect small body areas and thus result in less severe clinical phenotypes. Its etiology remains unknown and there is no molecular test to prove or disprove the diagnosis. Any proposed clinical

**Figure 1.** (A) Focal gigantism of the right thumb, distorted middle finger and amputation of the former index finger. (B) Right upper arm and forearm fatty subcutaneous overgrowth. (C) Right-hand radiograph demonstrating irregular, distorting bone growth and fused interphalangeal joint.
diagnostic criteria cannot be both sensitive and have a high positive predictive value; accurate diagnosis can be challenging, especially when clinical manifestations are limited.1

Table 1 Revised Proteus syndrome diagnostic criteria

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<thead>
<tr>
<th>Diagnostic criteria</th>
<th>General criteria</th>
<th>Specific criteria</th>
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<tr>
<td>Sporadic occurrence</td>
<td>(A)</td>
<td>Cerebriform connective tissue nevus</td>
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<tr>
<td>Mosaic distribution of lesions</td>
<td>(B)</td>
<td>1. Linear epidermal nevus</td>
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<td>2. Asymmetric, disproportionate overgrowth</td>
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<td>3. Specific tumours before second decade (either bilateral ovarian cystadenomas or parotid monomorphic adenoma)</td>
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<tr>
<td>Progressive course</td>
<td>(C)</td>
<td>1. Dysregulated adipose tissue</td>
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<td></td>
<td></td>
<td>2. Vascular malformations</td>
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<td>3. Lung cysts</td>
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<td>4. Facial phenotype</td>
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Adapted from Biesecker.1 All general criteria and specific criteria: either Category A, two from Category B or three from Category C.

Conclusions

Whether this case represents a delimited case of Proteus syndrome, a variant of CLOVE syndrome or an as yet uncharacterized overgrowth disorder remains unknown. Given the predicted variability of Proteus syndrome and the mosaicism model, we favour that diagnosis, but recognize that she does not quite meet the criteria, in the absence of confirmed cystadenomas.

A constellation of seemingly random physical features had been labeled random for 29 years. The challenges of clinical diagnosis in overgrowth disorders remain and the need for molecular diagnostic assays that could facilitate diagnosis is existent. The case highlights the importance of careful physical examination, which is of paramount importance in this context, as is accurate interpretation of physical findings.

Conflict of interest: None declared.

References