What is the diagnosis?

In view of the severe intellectual disability, behavioural and dysmorphic facial features, chromosome microarray (aCGH) was arranged for the child. aCGH showed a 3.39 Mb deletion in chromosome 17p11.2 (Figure 3), confirming the diagnosis of Smith Magenis syndrome.

What is Smith Magenis syndrome (SMS)?

SMS patients have distinctive physical and facial features including broad square-shaped face, brachycephaly, prominent forehead, synophrys, mildly upslanting palpebral fissures, deep-set eyes, broad nasal bridge, midfacial retrusion, short and full-tipped nose with reduced nasal height, micrognathia in infancy changing to relative prognathia with age, and fleshy everted vermillion of the upper lip. They have a hoarse and deep voice, language delay with or without associated hearing loss, variable levels of intellectual disability, signs of peripheral neuropathy, minor skeletal anomalies e.g. scoliosis, prepubertal short stature, brachydactyly and eye abnormalities. During infancy, they have feeding problems with failure to thrive, lethargy, hypotonia and hyporeflexia.1-3 The inverted diurnal circadian rhythm of melatonin is very typical in SMS.4

The behavioural problems usually appear from 18 months old, including self-mutilating behaviours by self-hitting, self-biting, skin picking, inserting foreign objects into body orifices (polyembolokoilamania) and pulling nails (onychotillomania). They also have autistic spectrum disorder, sensory integration problem, inattention, distractibility, externalising behaviours including hyperactivity, impulsivity, frequent temper outbursts and aggression. They have stereotypic behaviours with the typical spasmodic upper-body squeeze or “self-hug”, which is exacerbated by happiness, excitement or overstimulation.5-8 Over 50% of patients have hypercholesterolaemia.9

Virtually all SMS occur by de novo mutation. SMS is a contiguous gene deletion syndrome diagnosed clinically and confirmed by a 3.7 Mb heterozygous interstitial deletion in chromosome 17p11.2 in 90% of cases. A routine G-banded analysis with adequate resolution should detect the common deletion with 70% having the common approximately 3.5 Mb deletion. Deletion or mutation of the gene RAI1 (retinoic acid-induced protein 1) is responsible for many of the features in SMS.10, 11 Normal retinoic acid-induced protein 1 is thought to function in transcriptional regulation.12 FISH or aCGH is indicated for those strongly suspected to have SMS with previous normal results. The remaining 5-10% sequence variants can be confirmed by sequence analysis.13

Potocki-Lupski syndrome is a 17p11.2 duplication syndrome and contains the recombination reciprocal of the SMS deletion. Patients differ in their phenotypes and behaviours.14

Figure 3  aCGH result of the patient.
Clinical and diagnostic implication

The following workup needs to be done at diagnosis and include immunoglobulins, fasting lipid profile for monitoring of hypercholesterolaemia, thyroid function tests, spine radiographs, echocardiogram, renal ultrasound, ophthalmologic and otolaryngologic evaluation, neurodevelopmental assessment. For surveillance purpose, annual lipid profile, thyroid function, scoliosis, eye and hearing assessment is indicated.\(^2\)

Management

Management includes early childhood intervention programs, followed by ongoing special education programs, psychiatric medications for inattention and/or hyperactivity.\(^15\) For sleep problem, there were some treatment trials but they were not well-controlled.\(^16\) Adverse drug reaction with extreme aggression and escalation of behavioural problem was noted with atomoxetine for patients with Smith Magenis syndrome.

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References