ARTICLE

Van Maldergem syndrome: further characterisation and evidence for neuronal migration abnormalities and autosomal recessive inheritance

Sahar Mansour^{*1}, Marielle Swinkels², Paulien A Terhal², Louise C Wilson³, Philip Rich⁴, Lionel Van Maldergem⁵, Petra JG Zwijnenburg⁶, Christine M Hall⁷, Stephen P Robertson⁸ and Ruth Newbury-Ecob⁹

We present six patients from five unrelated families with a condition originally described by Van Maldergem *et al* and provide follow-up studies of the original patient. The phenotype comprises a distinctive facial appearance that includes blepharophimosis, maxillary hypoplasia, telecanthus, microtia and atresia of the external auditory meatus, intellectual disability, digital contractures and skeletal anomalies together with subependymal and subcortical neuronal heterotopia. Affected patients typically have neonatal hypotonia, chronic feeding difficulties and respiratory problems. In our cohort, we have observed one instance of sibling recurrence and parental consanguinity in three of the families, indicating that autosomal recessive inheritance is likely.

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INTRODUCTION

In 1992, Van Maldergem *et al*¹ described a girl with mental retardation, blepharo-naso-facial abnormalities and hand malformations. She was born to non-consanguineous parents and presented at birth with generalised hypotonia and a 'peculiar facial appearance'. She had bilateral auricular hypoplasia, camptodactyly of the third and fifth fingers with axially orientated clinodactyly of all five fingers, interdigital webbing and joint hyperlaxity. There was a partial choanal atresia. Significant feeding difficulties were present. She had moderate mental retardation with an IQ of 50. Her facial features were distinctive with telecanthus, epicanthus, a broad flattened nose, a large inverted W-shaped mouth and malformed ears. The presentation was not thought to be compatible with foetal alcohol teratogenicity despite a history of excessive exposure. On review at age of 11 years, she still had significant telecanthus but had developed a prominent nasal bridge with wide alae nasi. A G-banded karyotype was normal (46,XX). There is limited information on the radiological findings but these included maxillary hypoplasia with ocular hypertelorism and the hand radiograph showed a short fifth metacarpal. No cerebral imaging had been performed.

One further case was described by Zampino *et al*² and named the cerebro-facio-articular syndrome of Van Maldergem. They described a 5-year-old girl born to non-consanguineous parents who was

hypotonic with significant mental retardation who had similar facial dysmorphism. In addition, her mouth was held open, the upper lip had a trapezoidal configuration, the lower lip was everted and there was moderate micrognathia and low-set ears which were quadrangular in their morphology with hypoplastic lobes. She had camptodactyly of the third and fourth fingers bilaterally and foot deformities. A cerebral MRI demonstrated abnormalities of the corpus callosum and hypoplasia of the superior cerebellar vermis, the cerebellar tonsils, the pons and the optic chiasm. The frontal horns of the lateral ventricles were dilated with very significant reduction in the volume of the posterior white matter of both hemispheres.²

Subsequent to these descriptions, there have been no further published reports. We report six additional individuals (two siblings and four isolated cases) with this condition, as well as follow-up of the original case. The previously noted facial, auricular and limb components of the phenotype are confirmed, and furthermore a skeletal dysplasia and anomalous neuronal migration are also shown to constitute common but variable components of this phenotype. On account of the sibling recurrence and the observation that three of the six sets of parents were consanguineous, autosomal recessive inheritance seems the most likely mode of transmission of this disorder.

¹South West Thames Regional Genetics Service, London, UK; ² Department of Medical Genetics, University Medical Center, Utrecht, The Netherlands; ³ North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Trust, London, UK; ⁴Department of Neuroradiology, St George's Hospital NHS Trust, London, UK; ⁵Centre de Génétique Humaine, Université de Franche-Comté, Besançon, France; ⁶Department of Clinical Genetics VUMC, Amsterdam, The Netherlands; ⁷Institute of Child Health, London, UK; ⁸Department of Paediatrics and Child Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; ⁹Department of Clinical Genetics, St Michael's Hospital, Bristol, UK

*Correspondence: Dr S Mansour, South West Thames Regional Genetics Service, St George's Hospital NHS Trust, London SW17 0RE, UK. Tel: +44 (0)20 8725 0957; Fax: +44 (0)20 8725 3444; E-mail: smansour@sgul.ac.uk

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PATIENTS AND METHODS

In this study, seven patients with the clinical features of Van Maldergem syndrome (VMS) have been included. Each of these patients has been examined by at least one of the authors. A skeletal survey and brain MRI have been undertaken in six cases.

All patients had a normal karyotype after G-banding. Array CGH using varying methods (Affymetrix 500 k (Affymetrix, Santa Clara, CA, USA), Illumina Omni Quad 1.2 M (Illumina, San Diego, CA, USA), Agilent 180 k oligo array (Agilent Technologies, Wokingham, UK)) has been undertaken in all the patients. No abnormalities were identified. Screening of *FLNA* for point mutations, deletions or duplications by direct sequencing and MLPA was normal in all subjects. Very long-chain fatty acid and phytanic acid levels were normal in the first five cases (excluding Zellweger syndrome in view of the marked neonatal hypotonia).

RESULTS

Clinical data

Clinical details of patients are described below and summarised in Table 1. Photographs of patients are shown in Figures 1 and 2.

Patient 1 was a male infant born to non-consanguineous Caucasian parents at term following a normal pregnancy with a birth weight of 3.37 kg. Hypotonia, enlarged anterior fontanelle and hand abnormalities were noted. Due to tracheomalacia, he required a tracheostomy and assisted ventilation.

At 7 years of age, he was hypertelorism with short palpebral fissures, mild ptosis and a wide nasal bridge. The mouth had a tented upper lip, high palate with thickened gums, dental malocclusion, micrognathia, bilateral microtia with meatal atresia and conductive hearing loss were also present (Figure 1a and g). Camptodactyly and also a flexion deformity with palmar webbing of all the fingers was described (Figure 2a). He had a pectus deformity, sacral dimple, bilateral pes planus and a mild metatarsus adductus. There was moderate developmental delay. He required a gastrostomy for marked feeding difficulties. At 14 years, he had made considerable progress and had only mild to moderate learning difficulties consistent with a mental age of 7 or 8 years. He had developed significant dizzy spells on exertion, attributed to vestibular dysfunction. Renal ultrasound scans demonstrated small kidneys and he has a low/normal GFR. He has demonstrated a pitting oedema of the right hand, had persistent deciduous teeth and his stature was at the lower limit of normal range (-2.1 SD).

A skeletal survey showed a sclerotic base of the skull, with absent pneumatization of the sinuses and mastoid air cells. The frontal bone was markedly thickened and there were hypoplastic mandibular condyles and coronoid processes, narrow thorax, short clavicles, tall vertebral bodies with anterior scalloping in the upper lumbar region, subluxation of both radial heads and camptodactyly with flexion deformities of the fingers particularly at the proximal interphalangeal (PIP) joints. Radiographs of the hand indicate undermodelled 'S'-shaped metacarpals, the fourth being shortened. There was a generalised coarse trabecular pattern indicative of osteopenia.

Brain MRI demonstrated extensive subependymal grey matter heterotopia (bilateral nodular periventricular heterotopia (BNPH)) adopting a laminar appearance in the occipital and temporal horns of the lateral ventricles (Figure 4a and b). The corpus callosum was mildly dysmorphic being more curved than usual with a slightly thicker genu than splenium. The brainstem, cerebellum and pituitary gland were all normal (Figure 4c). The frontal, occipital and sphenoid bones were thickened with complete failure of aeration of all the paranasal sinuses.

Patient 2 was born to otherwise healthy parents who were first cousins of British ancestry. She was delivered by caesarean section at 32 weeks owing to maternal pre-eclampsia and had a birth weight of

1.8 kg (-0.3 SD). Hypotonia and facial dysmorphism were noted from birth with bitemporal narrowing, flat supra-orbital ridges, epicanthic folds, blepharophimosis, a small mouth and small undermodelled ears with atretic external canals (Figure 1b, h and i). Both anterior and posterior fontanelles were large. She required a tracheostomy for tracheomalacia, long-term nasal CPAP and a gastrostomy for feeding difficulties. Her anus was anteriorly placed. There were marked flexion deformities of all of her fingers (Figure 2b and c). There was delayed eruption of overcrowded teeth with malocclusion. She developed a severe kyphoscoliosis with spondylolysis at L5/S1, requiring surgery at the age of 9 years. Conductive deafness was demonstrated. She has mild learning difficulties. There is no history of seizures.

Skeletal survey showed brachy-turricephaly but no craniosynostosis. There was bony thickening of the base of the frontal bone but no sclerosis of the base of the skull. The maxilla was hypoplastic with a relatively normal mandible resulting in an underbite. The thorax was long and narrow with slightly short clavicles. There was an abnormal tilt of the pelvis with hip subluxation and malformation of some sacral vertebrae in addition to L5/S1 spondylolisthesis. The radial heads were subluxed. The hand radiographs confirmed fixed flexion deformities particularly of the PIP joints. The third and fourth metatarsals were short. There was generalised osteopenia (Figure 3a–d). MR imaging of the brain (Figure 4d–f) showed symmetrical, confluent subependymal heterotopic grey matter lining the lateral walls of both temporal horns from their anterior tip to the occipital horns. Heterotopic tissue was asymmetric, being more nodular in appearance on the left. In addition, there were also linear lesions within the walls of the bodies of the lateral cerebral ventricles that are iso-intense with grey matter and probably represent grey matter heterotopia. There were broad gyri in the temporal lobes posteriorly in addition to regions of cortical thickening suggestive of pachygyria interspersed with normal-appearing cortex.

Patient 3, a female baby born at term to first cousins of Caucasian origin was conceived by *in vitro* fertilisation and had normal birth parameters (weight 3.74 kg; $+1.1$ SD). Narrow choanae, wide cranial sutures, small ears, camptodactyly of the fingers and toes and a coccygeal appendage were noted soon after the birth. She was hypotonic and required a Nissen fundoplication and gastrostomy because of severe gastroesophageal reflux and persistent feeding difficulties. Failure to thrive resulted in growth parameters at -2.5 SD for height and weight and -2 SD for OFC at the age of 2 years. Craniofacial dysmorphism included a wide anterior fontanelle, bitemporal narrowing, short upslanting palpebral fissures with mild ptosis, prominent eyes, strabismus, thickened narrowed nares, high-arched palate, thickened alveolus, thin upper lip with downturned corners, a tongue tie and small ears (Figure 1c and j). She had single palmar creases, short tapered fingers with camptodactyly and fixed flexion at the PIP joints with single creases on the digits (Figure 2d). Examination of her genitalia indicated incomplete fusion of the labia minora. There was a postural scoliosis and a persisting caudal appendage. Her development was moderately delayed. Seizures were never observed. Renal ultrasound confirmed small but structurally normal kidneys and the echocardiogram was normal. Microlaryngo-bronchoscopy showed no structural abnormalities but there was laryngeal incoordination on dynamic imaging. On skeletal survey performed at 2 weeks of age, a narrow chest with short clavicles was noted, without any other apparent major change. MRI of the brain and spine (Figure 4g–i) showed nodular subependymal grey matter heterotopia bilaterally in the bodies and occipital horns of the lateral ventricles. Additionally, there was a continuous band of white matter

Table 1 A comparison of the clinical, radiographic and MRI brain findings in VMS

Gender	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7 Van Maldergem <i>et al</i> ¹		Zampino <i>et al</i> ²	
	Male	No	Female	First cousins	Female	First cousins	Male	Distant cousins	Male	Distant cousins	Male	No	Female	No	Female	No
Parental consanguinity	+		+		+		+		+		+		+		+	
<i>Craniofacial features</i>																
Large fontanelle	+		+		+		+		+		+		+		+	
Blepharo-nasal malformation	+		+		+		+		+		+		+		+	
Micrognathia	+		+		+		+		+		+		+		+	
<i>Limb anomalies</i>																
Camptodactyly with fixed flexion deformities	+		+		+		+		+		+		+		+	
Palmar/plantar interphalangeal webbing	+		+		–		+		+		Mild		+		–	
<i>Ear abnormalities</i>																
Bilateral microtia with conductive hearing loss	+		+		+		+		+		+		+		Small ears	
<i>Upper airway obstruction</i>																
Choanal atresia/stenosis	–		–		+		+		+		Suspected		+		–	
Tracheomalacia	+		+		LI		–		–		–		–		–	
Tracheostomy	+		+		–		+		+		–		–		–	
<i>Feeding difficulties</i>																
Gastrostomy	+		+		+		+		+		+		+		NA	
<i>Neurodevelopmental</i>																
Infantile hypotonia	Marked		Marked		Marked		NA		NA		+		+		+	
Developmental delay	Mild/moderate		Mild/moderate		Moderate		Mild		Moderate		Mild/moderate		Severe		Severe	
Other abnormalities	Small kidneys, reduced eGFR		Anterior anus, spondylosis, self-injurious behaviour		Small kidneys, caudal appendage		Small kidneys, anal stenosis, talipes, equinovarus		Anal stenosis, PS, hypospadias		Small kidneys with nephrocalcinosis		Self-injurious behaviour, no puberty (age 30 years), pectus deformity		Constipation, ataxia	
<i>Radiological features</i>																
Sclerotic base of skull	+		–		–		–		–		NA				NA	
Thickened frontal bone	+		+		–		+		+		NA				NA	
Hypoplastic mandibular condyles	+		–		–		–		–		NA				NA	
Maxillary hypoplasia	–		+		–		+		+		NA				NA	
Narrow thorax with short clavicles	+		+		+		–		+		+				+	
Subluxation of radial heads	+		+		–		–		+		NA				NA	
Generalised osteopenia	+		+		–		–		–		+					
<i>MRI brain findings</i>																
Migration abnormality	BNPH		BNPH		Double cortex		None		Bilateral laminar periventricular heterotopia		None		No MRI		Hypoplastic CC, asymmetrical ventriculomegaly	
Other abnormalities	Dysmorphic CC		Normal		Dysmorphic CC		Hypoplastic CC		Thinned CC		Agnesis of the CC				Hypoplastic cerebellar vermis and hemispheres	

Abbreviations: BNPH, bilateral nodular periventricular heterotopias; eGFR, epidermal growth factor receptor; CC, corpus callosum; LI, laryngeal incoordination; MRI, magnetic resonance imaging; NA, not available; PS, pulmonary stenosis; VSD, ventricular septal defect.

Figure 1 Facial characteristics of VMS. (a) patient 1 (b) patient 2 (c) patient 3 (d) patient 4 and (e) patient 5 (f) patient 6. The faces are characterised by blepharophimosis, telecanthus, a broad nasal bridge, flat facial profile (maxillary hypoplasia) and a progressive thickening of the alae nasi. Three subjects (patients 1, 2 and 5) required a tracheostomy due to airway collapse. (g–l) auricular anomalies in VMS. (g) patient 1; (h) and (i) patient 2; (j) patient 3; (k) patient 5 and (l) patient 6. There is microtia with thickening sometimes cystic of the crura and superior and inferior helical folds and atresia of the external auditory meatus with mixed conductive and sensorineural hearing loss.

Figure 2 Digital abnormalities camptodactyly and palmar contractures and webbing in VMS. (a) patient 1; (b) and (c) patient 2; (d) patient 3 and (e) patient 4.

partitioning two layers of cortical grey matter that was more prominent posteriorly but did extend into the temporal lobes and also into the fronto-parietal regions. The residual white matter volume was reduced with patchy signal abnormality. The overlying cerebral cortex was formed with a simplified gyral pattern, more so

posteriorly than anteriorly, to the extent that the cortical surface was nearly smooth over the lateral and inferior surface of the temporal and occipital lobes. The corpus callosum was thin with an exaggerated upward curve. The cerebellum, pituitary gland and brainstem were all normal in appearance.

Figure 3 Radiographic anomalies in VMS. (a–d) Patient 2. (a) Brachy-turricephaly with relative maxillary hypoplasia and underbite. Cochlear implants are present. (b) Long, narrow thorax with a tracheostomy tube *in situ*. (c) Flexion deformities at the proximal interphalangeal joints, distal pointing of the terminal phalanges and soft tissue syndactyly. (d) Hypoplastic third and fourth metatarsals resulting in short third and fourth toes. Patient 5 (e–i). Large anterior fontanelle, widened metopic suture, thickened frontal bone, absent pneumatization of the mastoid air cells and a hypoplastic mandibular condyle. (g, h) Subluxation of the radial head; (i) camptodactyly with flexion deformities at the proximal interphalangeal joints, soft tissue syndactyly and a short fourth metacarpal.

Figure 4 MRI anomalies noted in individuals with VMS syndrome. (Patient 1 a–c) (a) axial T2 image showing extensive laminar heterotopia (arrowed) extending from the occipital into the temporal horns of the lateral cerebral ventricles; (b) patient 1; axial T2 demonstrating linear lesions iso-intense with cortical grey matter adjacent to the lateral walls of the bodies of the lateral ventricles; (c) patient 1; sagittal midline T1 demonstrating a mildly dysplastic corpus callosum but normal hindbrain and brainstem structures; (d–f) patient 2 (d) axial T2 showing thick bands of heterotopic grey matter extending along the entire inferolateral wall of the temporal horns of the cerebral ventricles (arrowed). Overlying these lesions posteriorly are localised areas of cortical thickening and gyral simplification indicative of pachygyria (asterisks); (e) axial T2 image showing linear heterotopic tissue similar to that depicted in (b) anteriorly in the bodies of the lateral ventricles (arrowheads); (f) (coronal T1 just posterior to the trigone) demonstrating bilateral periventricular heterotopia (PH) inferolaterally in the posterior horns (arrows); (g–i) MRI scan of case 3 at 18 months of age. (g) Coronal T2 slice demonstrating alternating bands of grey (*) and white (w) matter within the posterolateral cortex, (h) extending into the temporal lobes and around the anterior convexities of the cerebral cortex (arrowheads) although the appearances are less pronounced anteriorly; (i) nodular PH within the walls of the lateral ventricles. The cerebral cortex demonstrates a simplified gyral pattern, more so posteriorly than anteriorly. (j) Patient 5, axial T1 image demonstrating laminar PH lining the occipital horns and peritrigonal region of the ventricles (arrows).

Patients 4 and 5 are siblings born to distantly related parents from Yemen who have two further healthy children and whose first child, born prematurely at 7 months gestation, died within hours of birth for unknown reasons. Case 4, their second child, was born after an uneventful pregnancy. He was noted at birth to be hypotonic and dysmorphic with a large, anterior fontanelle, sacral dimple, anal stenosis and camptodactyly of the fingers with flexion deformities of the PIP joints. A craniofacial CT scan confirmed a subtotal stenosis of both choanae, requiring tracheostomy until the age of 4 years and a PEG catheter until the age of 8 years. He had a ventricular septal defect (VSD) and pulmonary stenosis. He had bilateral atresia of the external meati resulting in conductive hearing loss. At the age of 10 years, he was short (height -4.1 SD) but with normal weight and head circumference ($+0.5$ SD). He had downsloping palpebral fissures, epicanthic folds, bilateral microtia, a small tongue and full lips, a small palate with broad gums and irregular teeth (Figure 1d). His nose was flat and broad with small nostrils and a wide, thickened nasal bridge. He had persistent camptodactyly of the fingers (Figure 2e), laxity of the elbow joints and bilateral talipes equinovarus. He had mild developmental delay and there was no history of seizures. Radiographs showed generalised osteopenia. The frontal bone was thickened but not sclerotic. There was no sclerosis of the cranial base. There was maxillary hypoplasia with a relatively normal mandible resulting in an underbite. The hand radiographs showed broad, undermodelled metacarpals with thin cortices. There were flexion deformities particularly at the PIP joints. Brain MRI during infancy showed a slightly enlarged ventricular system, a mildly hypoplastic corpus callosum but no detectable neuronal migrational anomalies. Ophthalmological examinations were normal. Renal ultrasound demonstrated bilateral small kidneys with large adrenal glands.

Patient 5, the fifth child of these parents, was born following an unremarkable pregnancy. At birth he was noted to be dysmorphic (Figure 1e) with multiple congenital abnormalities including choanal atresia, pulmonary stenosis and anal stenosis. His anterior fontanelle was large. He had bilateral microtia (Figure 1k). He also had hypospadias and a sacral dimple. There was camptodactyly of the second to fifth fingers (Figure 2e), talipes equinovarus and small nails. He required a tracheostomy because of respiratory insufficiency and continuous oxygen for lung hypoplasia. He required a gastrostomy for feeding. He had moderate learning difficulties with conductive hearing loss. There was no history of seizure activity. A skeletal survey confirmed similar changes to his brother with a large anterior fontanelle and thickened but not sclerotic frontal bones. There was maxillary hypoplasia with an underbite and broad mandibular rami. The thorax was long and narrow with short clavicles. There was subluxation of the head of the right radius. The hand radiographs confirmed the camptodactyly with flexion deformities and short fourth metacarpals with undermodelling of the metacarpals (Figure 3e–i). MRI of the brain at 2 years (Figure 4j) showed bilateral laminar periventricular heterotopic grey matter. The heterotopic tissue extended along the lateral walls of the posterior body and trigone of each lateral ventricle, and around the tips of the occipital horns. A thicker layer of heterotopic grey matter was evident abutting the lining of the temporal horns and reaching the very anterior tips of each ventricle bilaterally. The heterotopia did not extend into the frontal horns. Additionally, the inferior vermis was underdeveloped and the corpus callosum was intact but thinned in appearance. The cortical gyri overlying these regions of heterotopia were normal. An ophthalmological investigation and a renal ultrasound were normal.

Patient 6 is the only child of non-consanguineous parents with no significant family history. He was born at term by normal vaginal delivery following a pregnancy complicated by maternal HELLP syndrome. The birth weight was 3.04 kg (-1 SD). He developed respiratory distress shortly after birth. A choanal atresia was suspected but a CT scan showed a patent nasopharyngeal passage and he did not require a tracheostomy. He was hypotonic and failed to thrive. He required a gastrostomy and PEG for poor feeding. The kidneys were small with evidence of nephrocalcinosis. At the age of 1 year he had mild to moderate developmental delay, height was -1 SD, weight -2.5 SD and head circumference -1.5 SD. The facial features were characteristic for this condition with a flat midface, hypertelorism, epicanthic folds, depressed, flat nasal bridge, bilateral microtia, small mouth, some webbing of the neck and camptodactyly of the fifth fingers with minimal interphalangeal webbing and fetal finger pads (Figure 1f and l). There was a bilateral conductive hearing loss of 40 dB. A Skeletal survey confirmed short, hypoplastic clavicles with a long narrow thorax, undermodelled long bones with some widening of the metaphyses, Coxa valga, narrow iliac wings with some hypoplasia inferiorly, fifth finger camptodactyly and hypoplastic, narrow distal phalanges. MRI of the brain demonstrated agenesis of the corpus callosum with colpocephaly but no migrational abnormalities.

Patient 7 is the female who was originally reported by Van Maldergem *et al.*¹ She is now 32 years old and was placed in an institution for the mentally handicapped from the age of 8 years. She has been diagnosed with autism, with hand stereotypies, no language and severe intellectual disability. She remains dependent on professionals for activities of daily life. From the age of 20 years, self-injurious behaviour was noted. When examined at the age of 30 years, no breast development or secondary sexual characteristics had developed and she has not had menarche. Her height is -2 SD, her OFC -2.2 SD. The previously described distinctive clinical features, including small underdeveloped pinnae, epicanthus and camptodactyly were still present. In addition, she had developed a pectus deformity (excavatum and carinatum). No brain imaging is available.

DISCUSSION

This report presents six further individuals with the condition first described by Van Maldergem in 1992, together with an update on the original patient. The key clinical features include a combination of a distinctive facial appearance with limb anomalies, skeletal dysplasia and neuronal migration abnormalities and are summarised in Table 1.

Craniofacial features

Dysmorphic features evolve in the first year of life and include delayed closure of the fontanelles, small ears, a flat facial profile due to maxillary hypoplasia, phimosis of external auditory canal and nostrils, short palpebral features and telecanthus. The dentition is often irregular and three patients were noted to have thickened gums. Although choanal atresia was a major feature in the first report, it is not invariable. Three of the subjects described here exhibit upper airways obstruction sometimes requiring tracheostomy. The level of obstruction varies between individuals being attributed to subglottic narrowing or tracheomalacia.

Limb anomalies

The hand abnormalities are consistent and comprise camptodactyly at the PIP joints with palmar and interdigital webbing in some, and clinodactyly. Similar changes are found in the feet and talipes equinovarus is a variable additional finding.

Clinical course

Generalised neonatal hypotonia with significant feeding difficulties requiring long-term gastrostomy is characteristic of this condition. Investigations in one patient showed laryngeal incoordination and gastro-oesophageal reflux requiring fundoplication. Respiratory difficulties and insufficiency appear to be frequent.

Radiological features

The radiological features in childhood include generalised osteoporosis with large fontanelles and wide cranial sutures but often with sclerosis of the base of the skull. There is progressive thickening of the frontal bones but no accompanying sclerosis. The mastoids and sinuses are often under-aerated. The thorax is narrow with a flat diaphragm and short clavicles. Radiographs of the hands show a progressive widening and undermodelling of the metacarpals. The iliac wings are narrow and subluxation of the radial heads is commonly observed.

Neuronal migration abnormalities

MR imaging of the brain demonstrated neuronal migrational abnormalities in four of the six subjects evaluated by this modality. The most consistent and conspicuous anomaly was bilateral subependymal grey matter heterotopia. In one individual, laminar subcortical grey matter lesions were also observed in a pattern reminiscent of a subcortical band heterotopia.³ In two individuals, the subependymal heterotopia was nodular in appearance, whereas in others the heterotopic grey matter adopted a laminar appearance particularly in posterior and infra-sylvian regions of the brain. The subependymal heterotopia predominated in the posterior horns of the lateral ventricles and extended into the temporal horns inferolaterally although nodules were also observed in the bodies and, in one individual, in the anterior horns. In three individuals the heterotopic tissue abutting the lateral wall of the ventricular bodies adopted a tram-track-like appearance. Several entities characterised by periventricular nodular heterotopia have been outlined⁴ with one condition exhibiting laminar PH as shown here in cases 1, 2 and 4. Some regions of the posterior cortex with prominent regions of underlying laminar subependymal nodular heterotopia exhibited patches of pachygyria, something that was also a feature of the laminar PH syndrome described by Parrini *et al.*⁴ These individuals, however, had epilepsy and did not manifest the extra-neurological features described in this report. The neurodevelopmental consequence of these anomalies ranges from mild to moderate neurodevelopmental delay with the notable absence of any report of seizure activity.

Other findings

The affected siblings we reported both had pulmonary stenosis and one had a VSD but cardiac abnormalities were not observed in the remaining patients. The siblings were also noted to have anal stenosis and one further patient had an anteriorly placed anus. Four patients were noted to have small kidneys on renal ultrasound, with evidence of nephrocalcinosis in one. One patient had a caudal appendage. One male patient had hypospadias, whereas one female had partial fusion of the labia minora.

Differential diagnosis

This condition is sufficiently distinctive for it not to be readily confused with other described clinical entities. Winter–Tsukahara syndrome (pachygyria, joint contractures and facial abnormalities) lies within the differential diagnosis for VMS.⁵ Winter *et al.*⁵ described

a male neonate, the result of a father–daughter mating, with dysmorphic features, joint contractures, cystic pinnae of the ears and pachygyria. The baby died at 3 h of age of respiratory insufficiency. A further case was described with similar findings including pachygyria but no microtia.⁶ In both cases the condition was lethal due to pulmonary hypoplasia. It is possible that this is an allelic condition to the entity described in this report.

Mutations in *FLNA* can lead to PH,⁷ but a posterior distribution of the heterotopia with extension into the temporal horns is seldom observed in this condition and the hand and ear anomalies have not been described in *FLNA*-associated conditions.⁴

The one instance of subcortical laminar heterotopia (patient 3; Figure 4g–i) raises the possibility of other causes of double cortex, (namely mutations in *DCX*³ and *LIS1*⁸) as differential diagnoses. The present condition is unlikely to be allelic to these disorders, however, as neither X-linked subcortical band heterotopia nor mutations at the *LIS1* locus are associated with the facial, digital or auricular defects shown here.⁹ Array CGH and mutation analysis of *DCX* were negative in patient 3, further supporting mutations at a locus distinct from those implicated in those disorders as causative of this condition. Similarly, other conditions and chromosomal disorders occasionally associated with double cortex¹⁰ are unlikely to be conflated with this condition on clinical grounds.

Frank ter Haar syndrome,¹¹ another autosomal recessive condition, was considered in view of the apparent hypertelorism and caudal appendage in patient 3; however, the characteristic eye (anterior segment defects), cardiac (PDA, VSD) and skeletal anomalies (irregular ribs, wormian bones) associated with Frank ter Haar were not seen in this cohort. The hand and ear abnormalities seen in this group of patient has not been described in Frank ter Haar syndrome.¹²

Pashayan and Pruzansky described a family with blepharo-naso-facial malformations similar to those described in our patients. However, the lacrimal duct obstruction and torsion dystonia described in this condition were not seen in our cohort and the hand and ear abnormalities described here have not been described in association with BNF malformation.¹³

We conclude that VMS is a distinct and recognisable autosomal recessive condition with characteristic dysmorphic features, abnormalities in the hands and feet, radiological changes, neuronal migrational abnormalities on brain MRI and neonatal course.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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