Original Article

Mixed vascular nevus syndrome: a report of four new cases and a literature review

Martino Ruggieri[1], Agata Polizzi[2,3], Serena Strano[1], Carmelo Schepis[4], Massimiliano Morano[1], Giuseppe Belfiore[5], Stefano Palmucci[6], Pietro Valerio Foti[6], Concetta Pirrone[7], Vito Sofia[8], Emanuele David[9], Vincenzo Salpietro[10], Kshitij Mankad[11], Pietro Milone[12]

[1]Unit of Rare Diseases of the Nervous System in Childhood, Department of Clinical and Experimental Medicine, Section of Pediatrics and Child Neuropsychiatry, University of Catania, Catania, Italy; [2]National Centre for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy; [3]Institute of Neurological Sciences, National Research Council, Catania, Italy; [4]Unit of Dermatology, IRCCS Oasi M. Santissima, Troina, Italy; [5]Unit of Pediatric Radiology, [6]Department of Radiology, AOU "Policlinico-Vittorio Emanuele", Catania, Italy; [7]Department of Educational Sciences, Section of Psychology, [8]Department of Medical and Surgical Sciences and Advanced Technologies "G. F. Ingrassia", Section of Neurology, University of Catania, Catania, Italy; [9]Department of Biomedical Sciences and Morphologic and Functional Imaging, Policlinico "G. Martino", University of Messina, Messina, Italy; [10]Department of Molecular Neurosciences, University College of London, London, UK; [11]Unit of Pediatric Neuroradiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [12]Department of Medical and Surgical Sciences and Advanced Technologies "G. F. Ingrassia", Section of Radiology, University of Catania, Catania, Italy

Correspondence to: Martino Ruggieri, BA, MD, PhD. Unit of Rare Diseases of the Nervous System in Childhood, Department of Clinical and Experimental Medicine, Section of Pediatrics and Child Neuropsychiatry, University of Catania, AOU "Policlinico-Vittorio Emanuele", Presidio "G. Rodolico", Via S. Sofia 78, 95124 Catania, Italy. Email: m.ruggieri@unict.it.

Background: Mixed vascular nevus (or nevus vascularis mixtus) represents an admixture of cutaneous vascular malformations of the telangiectatic type and angiospastic spots of nevus anemicus. It can occur as an purely cutaneous trait or as a hallmark of a neurocutaneous phenotype (mixed vascular nevus syndrome) characterised by the combination of: (I) paired vascular (telangiectatic and anemic) twin nevi and brain abnormalities of the Dyke-Davidoff-Masson type (i.e., crossed cerebral/cerebellar hemiatrophy with hypoplasia of the ipsilateral cerebral vessels and homolateral hypertrophy of the skull and sinuses (hyperpneumatisation) with contralateral hemispheric hypertrophy); or (II) paired vascular twin nevi and brain malformations of the Dyke-Davidoff-Masson type in association with systemic abnormalities consisting in facial asymmetry, skeletal anomalies (i.e., Legg-Calvé-Perthes-like disease) and disorders of autoimmunity (i.e., diabetes, thyroiditis). In 2014, Happle proposed to name the syndrome with the eponym Ruggieri-Leech syndrome.

Methods: Review of the existing literature on nevus vascularis mixtus and information on our personal experience on new cases and follow-up of previously reported cases by some of us.

Results: The existing literature revealed 4 previous studies including 33 cases with an inferred purely cutaneous trait and 3 cases with a combination of paired vascular twin nevi and brain malformation of the Dyke-Davidoff-Masson type. Our personal experience includes 4 unpublished patients (1 female and 3 males; currently aged 2 to 34 years) seen and followed-up at our Institutions in Italy who had: paired vascular nevi involving either the face (n=2) or the face and parts of the body (n=2); facial asymmetry (n=4); mild to moderate facial dysmorphic features (n=2); developmental delay (n=3); seizures/stroke-like episodes and associated hemiplegia (n=4); muscular hypotrophy (n=2); mild to moderate hemispheric atrophy (n=4); skull osseous hypertrophy (n=4); hyperpneumatisation of the sinuses (n=2); hypoplastic brain vessels (n=4); colpocephaly and malformation of cortical development (n=2). Follow-up data on our previous 2 cases revealed that the vascular abnormalities in the skin and nervous system were stable over years without neurological progression or deterioration.

Conclusions: Pathogenically, this complex phenotype suggests that embryonic pairing and somatic

recombination of recessive (didymotic) alleles controlling the balance between constriction (i.e., nevus anemicus) and dilatation (i.e., nevus telangiectaticus) of blood vessels could be the primary event causing the phenomena of cutaneous and brain vascular twin spotting and the paired phenomena of skull hyperpneumatisation *vs*. hypertrophy and brain megalencephaly/colpocephaly *vs*. cortical dysplasia. This association is likely more frequent than previously thought and should be investigated by means of: (I) brain and spinal cord imaging (combination of CT and MRI studies); (II) skeletal X-ray studies (when dictated by clinical findings); (III) systemic ultrasound studies; (IV) neurophysiologic studies (EEG); (V) psychomotor testing; (VI) and laboratory investigation (including immune-mediated dysfunction).

Keywords: Mixed vascular nevus; nevus vascularis mixtus; mixed vascular nevus syndrome; telangiectatic nevus; nevus anemicus; Dyke-Davidoff-Masson syndrome; magnetic resonance imaging (MRI); computerised tomography (CT); ultrasound; EEG

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Introduction

The term mixed vascular nevus (or nevus vascularis mixtus) refers to the admixture of cutaneous vascular malformations of the telangiectatic type and angiospastic spots of nevus anemicus (1). These are vascular nevi of the capillary type (1-4). Telangiectatic nevi are congenital skin lesions formed by small, dilated blood capillaries measuring 0.5–1 mm in diameter; these lesions may show areas of normal tissue within the affected area, intermingled with involved areas, leading to a somewhat reticular pattern with preserved irregular borders (2-4). The so-called nevus anemicus represents a vasoconstrictive counterpart of telangiectatic nevi; typically, it is a pale macule with a highly irregular margin. If the skin is rubbed, there is no erythematous reflex within the nevus (1-4). Both nevi may occur as pure cutaneous traits (1-6) or as a part of several genetic skin disorders (6) including phacomatosis pigmentovascularis (PPV) (e.g., phacomatosis cesioflammea and cesioanemica) (7-10) and a newly reported phenotype known as mixed vascular nevus (nevus vascularis mixtus) (1,6,10-12).

Mixed vascular nevus (nevus vascularis mixtus)

This complex dermatologic vascular malformation was initially recognized and comprehensively described by Hamm and Happle in 1986 (1), who reported their personal experience in 4 cases (one child and 3 young adults) and summarized 28 cases (aged 1 to 49 years) that were collected from the literature from 1909 to 1952 (1). They first hypothesized (1) that the combination of these vascular nevi (originally described as "telangiectatic nevus" and its "angiospastic part" (i.e., the nevus anemicus), situated directly adjacent one to each other, could not be regarded as an incidental finding but represented a distinct entity and named it "naevus vascularis mixtus" (1,6). In subsequent reports, Happle (13,14) called these lesions "vascular twin nevi". In his latest classifications of the various archetypical shapes and patterns of cutaneous nevi, Happle (2-4) categorized the telangiectatic nevus (as well as the nevus anemicus) into the configurations called "patches with indented borders" and "blocks or flags" stating that "lesions adopting these shapes may show areas of normal tissue within the patch, intermingled with involved areas, leading to a somewhat reticular pattern with preserved irregular borders" (2-4). Di Lernia *et al*. (5) and Happle (14) further defined this skin phenotype understanding that it was characterised by a true admixture of reticular telangiectatic lesions and angiospastic spots of nevus anemicus.

Mixed vascular nevus syndrome

In 2012, some of us (12) reported two individuals with a combination of these paired cutaneous vascular malformations (of the reticular telangiectaticus nevus and angiospastic nevus anemicus types) (nevus vascularis mixtus or paired vascular twin nevi) (*Figure 1*) coupled with brain abnormalities of the Dyke-Davidoff-Masson type (i.e., crossed cerebral/cerebellar hemiatrophy with hypoplasia of the ipsilateral cerebral vessels and homolateral hypertrophy of the skull and sinuses (hyperpneumatisation) with contralateral hemispheric hypertrophy) (15) in association

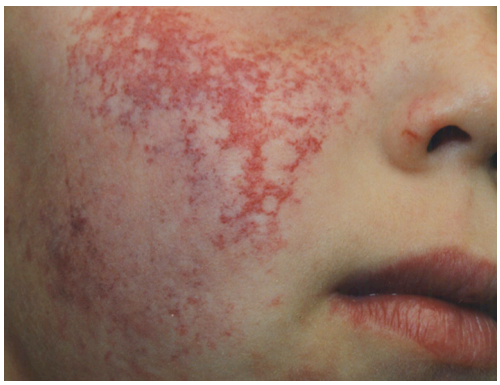

Figure 1 Note a telangiectatic nevus in close proximity to a nevus anemicus in a background of normal complexion (the nevus anemicus is paler in the inner area, which is surrounded by dotted erythematous adjacent skin).

with systemic abnormalities consisting in facial asymmetry, skeletal anomalies (i.e., Legg-Calvé-Perthes-like disease) and disorders of autoimmunity (e.g., diabetes, thyroiditis).

In 2014, Happle (10) proposed to name this complex malformation phenotype with the eponym *Ruggieri-Leech* syndrome melting the first report where the pure paired cutaneous trait (i.e., mixed vascular nevi) was associated to extra-cutaneous manifestations (10) to a previous report by Leech *et al*. (11), who coupled a capillary malformation identical to the mixed vascular nevus (but not yet understood and/or labelled as nevus vascularis mixtus) to a brain malformation of the megalencephaly type (i.e., similar to the phenomena of increased growth seen in the Dyke-Davidoff-Masson syndrome).

Methods

Patients

Patients were selected from the database of neurocutaneous disorders at the University of Catania. Each patient underwent full clinical and laboratory examination, including general, dermatological, ophthalmological and neurological examination and full laboratory investigation including ECG, heart ultrasound, abdominal and pelvic ultrasound examination, standard- and video-EEG, and X-ray films when dictated by clinical findings. All patients underwent magnetic resonance imaging studies of the central nervous system using Signa-HDdxt 1.5 Tesla (G.E. Healthcare, Milwaukee, USA) with T1, T2, T2-FLAIR, and MRA sequences. CT scans were obtained using Optima CT660 (G.E. Healthcare, Milwaukee, USA) with spiral multi-slice technique. The local ethics committee (Comitato Etico 1, University of Catania) approved this retrospective analysis and reporting. Patients' consent was obtained (and/or waived due to the non-interventional retrospective analysis nature of this study).

Literature review

Studies published in the literature (Medline, Scopus, WOS and bibliographies) reporting on the coexistence of nevus anemicus and nevus telangiectaticus in association or not with neurological involvement and mixed vascular nevus syndrome were reviewed (all years). Literature search was performed by using the following key words: "nevus anemicus", "nevus telangiectaticus", "nevus vascularis mixtus", "mixed vascular nevus syndrome", "Dyke-Davidoff-Masson syndrome", "neurological", "nervous system", and "MRI": were considered studies reporting data in English, German, French and Spanish.

Results

Patients

We identified 4 patients (3 males, 1 female; currently aged 2 to 34 years; median age =13.75 years) who had the coexistence of nevus anemicus and nevus telangiectaticus (mixed vascular nevi) in association with extra-cutaneous features including neurological and systemic manifestations first seen and followed-up (mean follow-up =8 years) at the University of Catania. The main clinical, laboratory and imaging findings are summarised in *Table 1* and illustrated in *Figures 2-4*.

Literature review

Literature review revealed 110 results whose clinical reports contained information regarding the coexistence of nevus anemicus and nevus telangiectaticus. Only 4 out of these 110 studies (1,6,10,13) contained information regarding the spatial and temporal admixture of a mixed vascular nevus in association (10,13) or not (1,6) with extra-cutaneous features. Hamm and Happle (1) collected information on 28 cases (aged 1 to 49 years) from the literature and personally examined four additional cases. We identified 2 studies (10,13), including our previous study (10) on two patients with mixed vascular nevus syndrome

Table 1 Clinical findings in 4 patients with mixed vascular nevus syndrome

Main features	Patient 1	Patient 2	Patient 3	Patient 4
Gender	F	M	M	M
Age	2	7	12	34
Growth parameters				
Height	50th	75th	50th	90th
Weight	75th	50th	50th	90th
OFC	50th	50th	50th	90th
Skin vascular malformation	NA, TN	NA, TN	NA, TN	NA, TN
Face	TN (R)	NA, TN (>L)	NA, TN (B)	NA, TN (B)
Trunk	NA, TN (B)	NA, TN (L)	–	–
Upper limbs	NA, TN (B)	NA, TN (L)	–	–
Lower limbs	TN (B)	NA, TN (foot)	–	–
Systemic features				
Coarse face	–	–	–	+
Facial asymmetry	+	+	+	+
Brushy eyebrows	–	+	–	+
Hypertelorism	–	–	–	+
Large/bulbous nose	–	+	–	+
Wide philtrum	–	–	–	+
Prominent/thick lips	–	–	–	+
Short neck	–	–	–	–
Other	–	–	–	Psoriasis
Neurologic features				
Developmental milestones	N	D	D	D
Epilepsy	+	+	+	+
Stroke-like episode (hemiplegia)	+	++	+	+++
Muscular hypotrophy	–	+	–	+
Headache	–	–	–	–
Other features				Epidermal nevus
Spectrum of Dyke-Davidoff-Masson				
Hemisphere atrophy	+ (R)	+ (R)	+ (R)	+ (R)
Contralateral cerebral hypertrophy	+	+	+	+
Skull osseous hypertrophy	+ (P, M)	+ (P, M)	+	+++ (R)
Hyperpneumatisation of sinuses	+	+	–	–
Hypoplastic brain vessels	WC	Carotid	AC	PC
Other	–	–	Colpocephaly, polymicrogyria	Colpocephaly (R), polymicrogyria
Array-CGH analysis	–	–	–	–

M, male; F, female; R, right; L, left; NA, nevus anemicus; TN, telangiectatic nevus; WC, Will's circle; AC, anterior communicating; PC, posterior communicating; Array-CGH, array comparative genomic hybridization.

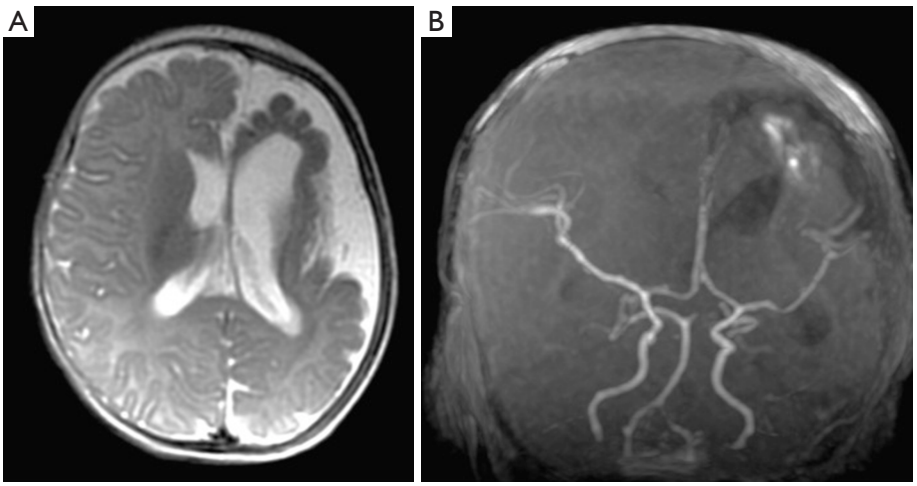

Figure 2 Patient 2 (*Table 1*): T2-weighted axial magnetic resonance image of the brain (A) showing atrophy of the left hemisphere with dilatation of the left ventricle and cortical dysplasia; magnetic resonance angiography of the brain (B) shows reduction in calibre of the left cerebral artery (especially the Sylvian artery).

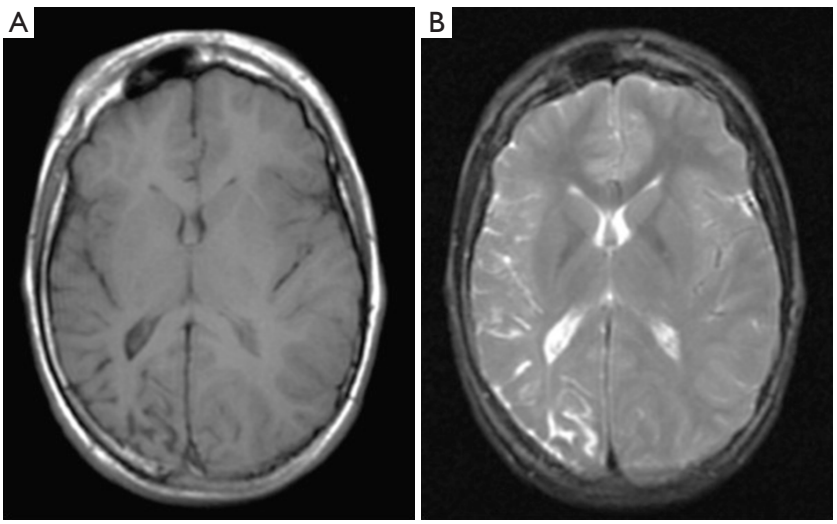

Figure 3 Patient 1 [as reported in reference (12): at his most recent follow-up] T1- (A) and T2- (B) weighted magnetic resonance images of the brain showing hyperpneumatisation of the right frontal sinus, atrophic right hemisphere and hypertrophic left hemisphere with cortical dysplasia (B).

(currently still under follow-up at our Institutions) for a total of 3 patients (2 M, 1 F) with mixed vascular nevus syndrome [see also reference (12)].

Mixed vascular nevus syndrome: definition of the neurocutaneous phenotype

By literature review (1,6,10-12) and personal experience [including data reported in *Table 1* and follow-up of patients reported in reference (12)] we aimed to better define the cutaneous and extra-cutaneous phenotype of the mixed vascular nevus syndrome as follows.

Cutaneous features

Co-occurrence of telangiectatic nevus and nevus anemicus situated directly adjacent one to each other (spatial and temporal admixture) (*Figure 1*). Notably, by literature review and personal experience we recorded these two dermatologic

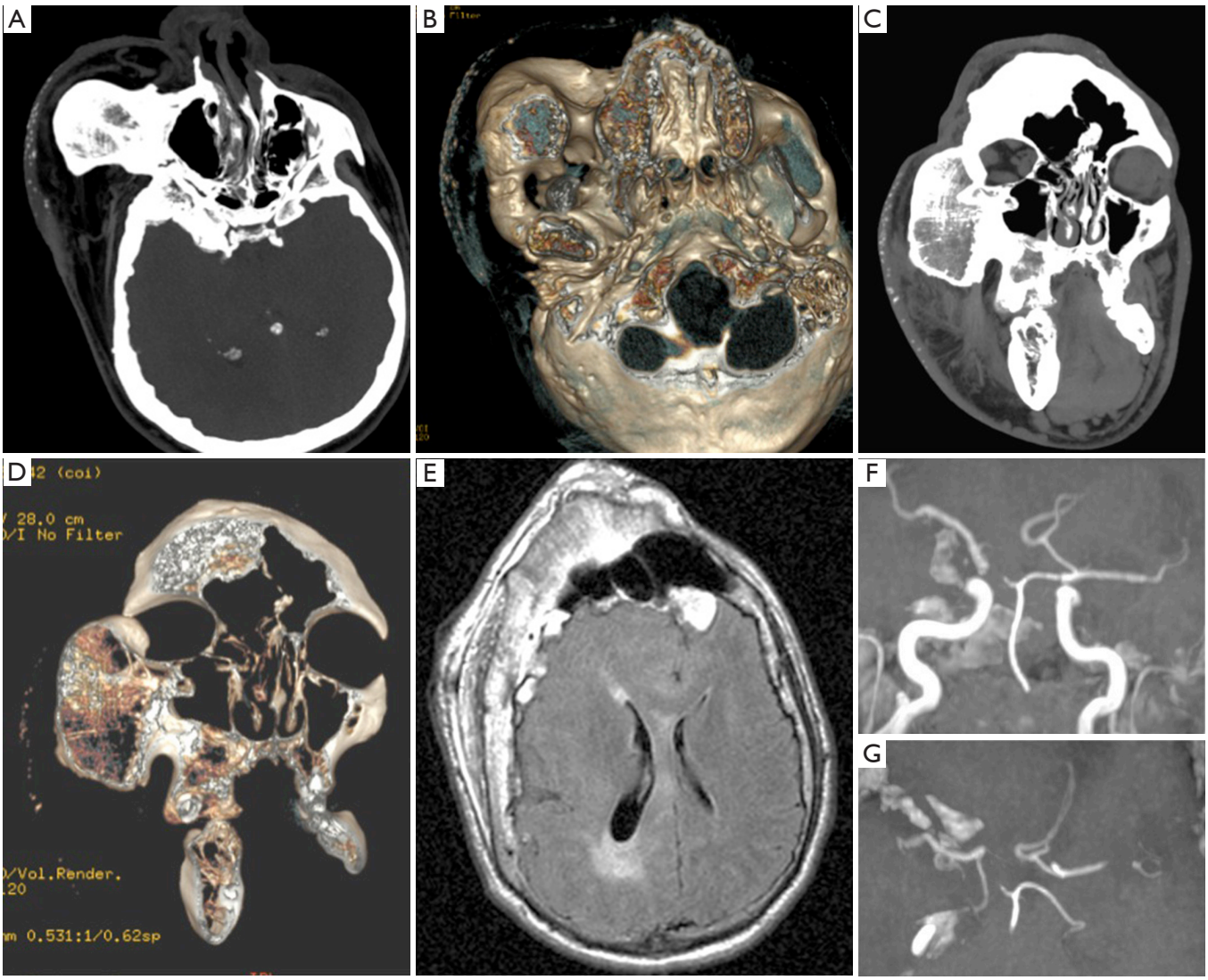

Figure 4 Patient 4 (*Table 1*): axial MIP (A) and volume rendering (B) and coronal MIP (C) and volume rendering (D) CT scan of the brain; axial T2-flair (E) magnetic resonance image of the brain; and brain MRA (F,G). Note the massive hypertrophy of the right skull with dotted calcifications of the soft tissues of the face (A-D); the complex right hemispheric ventricular and cortical malformation (E) and the anatomical variants of the inner circle with right A1 and P1 arteries hypoplasia. CT, computerised tomography.

traits adjacent or in close proximity one to each other or in distant areas with satellite macules (*Figure 1*): however, it is the contemporary presence in the same individual the skin hallmark of disease.

Typically, enhancement of the paler inner-dotted areas and satellite macules is usually demonstrated upon stroking (or applying heat or cold) to the nevus anemicus and adjacent skin, which became erythematous. Histological analysis from affected area shows wider capillaries' lumens lined with flat endothelial cells, without an increase in melanin pigmentation.

Neurological phenotype

There were mild to moderate developmental delay with cognitive deficits and behavioural abnormalities (usually hyperactivity and opposing behaviour), crossed alternating episodes of simple partial and/or hemiplegic seizures, and speech difficulties. There is no progression. Seizures, which in some cases, could be regarded as stroke-like episodes, are either secondary to the occasional vasoconstriction of the angiospastic/hypoplastic brain vascular vessels (see below), or, more frequently, secondary to the underlying

cortical brain malformation. Regardless to their nature and semiology, these paroxysmal events become less frequent after adolescence (unless associated to moderate to severe brain malformations: see also *Figure 4* and below).

Systemic abnormalities

These consist of (mild to moderate) facial asymmetry with facial dysmorphic features (e.g., rounded and coarse face with synophris, hypertelorism, a large and bulbous nose, a large philtrum with thin lips, and short neck), dental anomalies including irregularly shaped and malpositioned teeth, skeletal anomalies (i.e., Legg-Calvé-Perthes-like disease) and disorders of autoimmunity including diabetes and thyroiditis (12).

Brain imaging abnormalities

Brain computerised tomography (CT) and/or magnetic resonance imaging (MRI) usually reveals (*Figures 2-4*) asymmetry of the cerebral hemispheres with mild (*Figure 3A,B*) to moderate (*Figure 4E,F*) or severe (*Figure 2A*) hemispheric atrophy; ipsilateral osseous hypertrophy (*Figures 3,4*); hyperpneumatisation of the paranasal sinuses (and mastoid cells) (12) and contralateral cerebral hypertrophy (*Figure 3*). The cerebral circle is usually affected, ranging from mild (*Figure 2*) to moderate (*Figure 4*) degrees of dysplasia, including hypoplastic hemi-circle of Willis with hypoplasia of P1 and A1 cerebral arteries (*Figures 2B,4F,G*). The spectrum of brain abnormalities may include malformations of cortical development (*Figures 2-4*) with megalencephaly (*Figure 3*), dilated ventricles (colpocephaly), polymicrogyria and pachygyria (*Figures 2A,4E*) (11,12). The brain atrophy and ipsilateral vascular hypoplasia could be minimal (12). The degree of osseous hypertrophy could be impressive and extended to the frontal, maxillary and mandibular regions simulating an osseous dysplasia (*Figure 4A-D*) with somewhat dotted calcification of the soft tissues in the affected area with the cutaneous vascular malformation (*Figure 4A-D*) (*Table 1*).

Single photon emission computerized tomography (SPECT) study of the brain showed in one case (12) reduced blood perfusion in the atrophic brain hemisphere with normal flow in the middle portion of the frontal and occipital lobes.

Overlapping features and misdiagnoses with other neurocutaneous disorders associated to vascular malformations

The so-called phacomatosis pigmentovascularis (PPV) (7,10,16) is defined as the coexistence of a widespread vascular (usually capillary) nevus (nevus flammeus) and an extensive pigmentary nevus (usually of the Mongolian spot type or blue/slate/grey oculo-cutaneous melanocytosis) associated or not to a variety of other cutaneous nevi including nevus anemicus, nevus telangiectaticus, epidermal nevus, nevus spilus or cutis marmorata telangectasica and/or extra-cutaneous alterations. The various combinations of skin nevi are currently classified as (7): (I) PPV type I (capillary malformation + epidermal nevus; (II) PPV type II (type IIa: nevus flammeus and Mongolian spot; type IIb: IIa + nevus anemicus; (III) PPV type III (type IIIa: nevus flammeus and nevus spilus; type IIIb: type IIIa + nevus anemicus; (IV) PPV type IV (nevus flammeus and Mongolian spot and nevus spilus + nevus anemicus; (V) PPV type V (Mongolian spot and cutis marmorata telangiectatica congenita. An alternative classification (9) is based on five subtypes only classified according to the colour of nevi and follows the Latin nomenclature: (I) phacomatosis cesioflammea (caesius = blue grey of the Mongolian spot plus the nevus flammeus: i.e., identical to the traditional types IIa and IIb); (II) phacomatosis spilorosea (nevus spilus coexisting with a pale-pink telangiectatic nevus (nevus roseus, which is of a much lighter hue than nevus flammeus): i.e., corresponding to the traditional types IIIa and IIIb); (III) phacomatosis melanorosea (large café-au-lait spots coexisting with nevus roseus sometimes accompanied by cutis marmorata-like lesions); (IV) phacomatosis cesiomarmorata (blue spots and cutis marmorata telangiectatica: i.e., a descriptive term for PPV type V); and (V) phacomatosis cesioanemica (blue nevus coexisting with nevus anemicus): i.e., a variant of phacomatosis cesioflammea. Associated features involve the eye (melanosis bulbi, iris mammillations, megalocormea) and musculoskeletal (facial and limb overgrowth, macrocephaly and scoliosis) systems. As outlined above, phacomatosis cesioflammea and cesioanemica (2,17,18), which encompass within their phenotypes nevus anemicus and variants of nevus flammeus could be misdiagnosed as mixed vascular nevus syndrome, unless their pigmentary counterparts (i.e., blue-grey nevi of the Mongolian type) are well recognised.

Pathogenesis

A unifying didymotic theory: allelic *vs*. non-allelic twin spotting phenomena

Analogously to what occurs in other organisms, these phenotypes suggest that pairing and somatic recombination

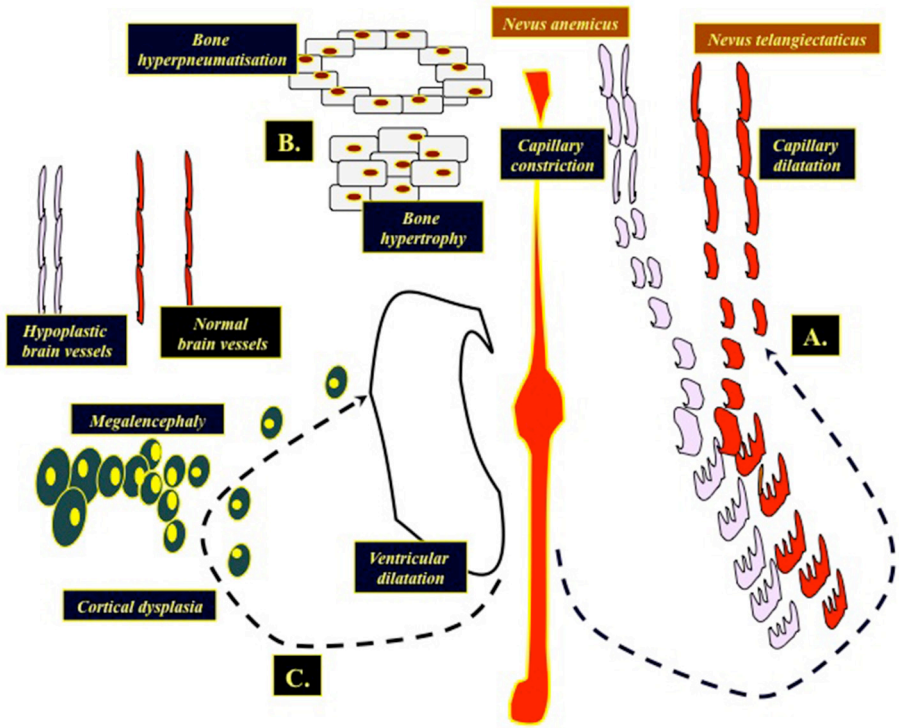

Figure 5 Drawing illustrating the unifying dydymotic theory as a pathogenic explanation for the mixed vascular nevus syndrome: (A) pairing and somatic recombination of recessive (didymotic) alleles controlling the balance between capillary dilatation (i.e., nevus telangiectaticus) *vs.* capillary constriction (i.e., nevus anemicus) of cutaneous blood vessels in an embryo acts as a primary event causing (as a secondary event) vascular twin spotting with the appearance of two neighbouring and partially admixed capillary cell populations (i.e., paired vascular twin nevi); (B,C) similarly to what occurs in the skin, the paired vascular twin spotting phenomena affecting the brain vessels (vascular hypoplasia *vs.* normal brain vessels), the bone (B) (i.e., hyperpneumatisation vs. hypertrophy) and the brain tissue (C) (megalencephaly/dilated ventricles *vs.* cortical dysplasia) may well represent dichotomic functional abnormalities likely reflecting allelism at the same underlying gene loci of the vascular twin nevi (in the middle of the drawing an example of a radial cell (in orange) used as a support by skin cells and neurons for climbing up to their final destination).

of recessive (didymotic) alleles controlling the balance between constriction (i.e., nevus anemicus) and dilatation (i.e., nevus telangiectaticus) of cutaneous blood vessels in an embryo could be the primary event causing twin spotting (i.e., paired vascular twin nevi) (*Figure 1*) and the appearance of the two neighbouring and partially admixed cell populations would be the secondary phenomenon (2-5,10). In addition to that, similarly to what occurs in the skin, the crossed hemi-cerebral malformation (*Figures 2-4*) may well represent dichotomic functional abnormalities likely reflecting allelism at the same, yet undiscovered, underlying gene loci of the vascular twin nevi (*Figure 5*). By taking into consideration all these events, we propose a unifying didymotic theory to explain the pathogenesis of cutaneous and extra-cutaneous phenomena in mixed vascular nevus syndrome: the dichotomic phenomena of capillary dilatation (in the skin and brain vessels), hyperpneumatisation of the sinuses (in the skull) and telangiectasia/ventriculomegaly *vs.* capillary constriction (in the skin and brain vessels, see *Figure 5A*), bone hypertrophy (in the skull, see *Figure 5B*) and cortical dysplasia/megalencephaly (see *Figure 5C*) may reflect paired phenomena affecting different tissues (1,19).

Management

Cosmetic facial alterations caused by the mixed vascular malformations can best be treated by sophisticated laser therapeutic techniques. The results are satisfactory in cases with capillary malformations of low pigmentation (12), with lightening of the pigmented zone [see case 2, reference (12)].

Seizures can be treated similarly to those in patients without mixed vascular nevus syndrome. Carbamazepine or oxicarbamazepine, valproic acid, topiramate, levitiracetam, hydantoins and clonazepam are the most used antiepileptic drugs (6,12). Patients with intractable seizures, benefit of combination of antiepileptic drugs. Low-dose aspirin (3–5 mg/kg/d) is used to optimize stroke-like episodes and neurodevelopmental outcome, as in Sturge-Weber syndrome, with minimal side effects (6,12,20).

Scoliosis (and/or other orthopaedic anomalies) and spasticity, when present, have been treated with physiotherapy, orthopaedic help or botulism toxin.

Problems at school that affect intellectual function and behaviour in most cases, may need special help and stimulants drugs, such as methylphenidate, associated with antiepileptic treatment.

Paired vascular twin nevi of the telangiectatic and anemicus types are likely more frequent than previously thought and should be investigated by means of: (I) brain and spinal cord imaging (combination of CT and MRI studies); (II) skeletal X-ray studies (when dictated by clinical findings); (III) systemic ultrasound studies; (IV) neurophysiologic studies (EEG); (V) psychomotor testing; (VI) and laboratory investigation (including immune-mediated dysfunction).

Conclusions

The nevi pigmentation is stable and the skin within the nevi area is firm over years: it can occasionally become dry and pruriginous. Overall, the skin complexion and texture are different from other vascular malformations syndromes (e.g., Sturge-Weber syndrome) without progression or hypertrophy of the soft tissues.

In our experience and after long-term follow-up, seizures and/or stroke-like events, regardless to their nature and semiology, become less frequent after adolescence (unless associated to complex underlying nervous system malformations). The psychomotor outcome is fine with good social integration. Brain imaging follow-up reveals no progression or vascular degeneration.

The autoimmune skin phenomena usually decrease with age and the immune-mediated systemic abnormalities respond to usual treatments.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the local ethics committee (Comitato Etico 1, University of Catania). Patients' consent was obtained (and/or waived due to the non-interventional retrospective analysis nature of this study).

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