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Multidisciplinary Outpatient Clinic of Neurocutaneous Diseases: Five-year Experience of a Pediatric Tertiary Hospital in Portugal

Consulta Multidisciplinar de Doenças Neurocutâneas: Experiência de Cinco Anos num Hospital Pediátrico Terciário em Portugal

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ABSTRACT

Introduction: Neurocutaneous syndromes (NCS) are a heterogeneous group of conditions with multiorgan involvement and diverse manifestations, evolving throughout life with significant morbidity. A multidisciplinary approach to NCS patients has been advocated, although a specific model is not yet established. The aim of this study was 1) to describe the organization of the recently created Multidisciplinary Outpatient Clinic of Neurocutaneous Diseases (MOCND) at a Portuguese pediatric tertiary hospital; 2) to share our institutional experience focusing on the most common conditions, neurofibromatosis type 1 (NF1) and tuberous sclerosis complex (TSC); 3) to analyze the advantages of a multidisciplinary center and approach in NCS.

Methods: Retrospective analysis of 281 patients enrolled in the MOCND over the first five years of activity (October 2016 to December 2021), reviewing genetics, family history, clinical features, complications, and therapeutic strategies for NF1 and TSC.

Results: The clinic works weekly with a core team of pediatrician and pediatric neurologist supported by other specialties as needed. Of the 281 patients enrolled, 224 (79.7%) had identifiable syndromes such as NF1 (n = 105), TSC (n = 35), hypomelanosis of Ito (n = 11), Sturge-Weber syndrome (n = 5), and others. In NF1 patients, 41.0% had a positive family history, all manifested *café-au-lait* macules, 38.1% neurofibromas with 45.0% being large plexiform neurofibromas. Sixteen were under treatment with selumetinib. Genetic testing was performed in 82.9% of TSC patients with pathogenic variants found in *TSC2* gene in 72.4% patients (82.7% if considered contiguous gene syndrome). Family history was positive in 31.4%. All TSC patients presented hypomelanotic macules and fulfilled diagnostic criteria. Fourteen patients were being treated with mTOR inhibitors.

Conclusion: Offering a systematic and multidisciplinary approach to NCS patients enables timely diagnosis, promotes a structured follow-up, and encourages discussion to outline management plans for optimal care to every patient, with significant impact on the quality of life of patients and families.

Keywords: Child; Neurocutaneous Syndromes/diagnosis; Neurocutaneous Syndromes/genetics; Neurofibromatoses 1; Outpatient Clinics, Hospital; Tuberous Sclerosis

RESUMO

Introdução: As doenças neurocutâneas (DNC) são um grupo heterogéneo de patologias com envolvimento multiorgânico e manifestações diversas que evoluem ao longo da vida, com morbilidade significativa. Tem sido preconizada uma abordagem multidisciplinar destes doentes, contudo o modelo ideal não está ainda estabelecido. Este trabalho tem como objetivos 1) descrever a organização da recém-criada Consulta Multidisciplinar de Doenças Neurocutâneas (CMDNC) de um hospital pediátrico terciário em Portugal; 2) partilhar a experiência institucional, focando as patologias mais comuns, neurofibromatose tipo 1 (NF1) e complexo esclerose tuberosa (CET); e 3) analisar as vantagens de um centro e abordagem multidisciplinares nas DNC.

Métodos: Análise retrospetiva dos 281 doentes acompanhados na CMDNC durante os primeiros cinco anos de funcionamento (outubro 2016 a dezembro 2021), com revisão da genética, história familiar, manifestações clínicas, complicações e estratégias terapêuticas dos doentes com NF1 e CET.

Resultados: A CMDNC funciona semanalmente com um pediatra e um neuropediatra, com apoio de outras especialidades sempre que necessário. Dos 281 doentes acompanhados, 224 (79,7%) têm síndromes identificados, como NF1 (n = 105), CET (n = 35), hipomelanose de Ito (n = 11), síndrome de Sturge-Weber (n = 5), e outras. Dos doentes com NF1, 41,0% têm história familiar positiva, todos apresentavam manchas 'café com leite', 38,1% neurofibromas, dos quais 45,0% com grandes neurofibromas plexiformes. Dezasseis estavam sob tratamento com selumetinib. Foi realizado estudo genético em 82,9% dos doentes com CET, com variantes patogénicas identificadas no gene *TSC2* em 72,4% (82,7% se considerado síndrome de genes contíguos). Em 31,4% havia história familiar positiva. Todos os doentes com CET apresentaram máculas hipomelanocíticas e cumpriam critérios diagnósticos. Catorze doentes estavam sob tratamento com inibidores mTOR.

Conclusão: Oferecer uma abordagem sistematizada e multidisciplinar nas DNC possibilita um diagnóstico atempado, promove um acompanhamento estruturado, e favorece a discussão para delinear um plano de cuidados adequado, com impacto significativo na qualidade de vida dos doentes e famílias.

Palavras-chave: Ambulatório Hospitalar; Criança; Doenças Neurocutâneas/diagnóstico; Doenças Neurocutâneas/genética; Esclerose Tuberosa; Neurofibromatose 1

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INTRODUCTION

Neurocutaneous syndromes (NCS), also known as phakomatoses, result from an anomaly in the formation, migration or differentiation of the neural crest, affecting the development of the neuroectodermis and therefore tissues derived from this structure, such as skin, central and peripheral nervous system and the eye.[1,2] The word phakoma was first used in 1932 by the ophthalmologist van der Hoeve to describe a 'mother lesion' or birthmark, which is a distinctive feature in most of these disorders.[3–5] The predisposition to tumor development is also a unifying aspect as the genetic basis of NCS mostly involves mutations in tumor suppressor genes or genes involved in cell growth and proliferation.[6] Organs such as kidneys, bones, heart, lungs, gastrointestinal tract, and teeth may also be involved. To date, more than 50 forms of NCS have been described. The diagnosis can be made through genetic testing or, for some conditions such as neurofibromatosis (NF1) and tuberous sclerosis, by clinical criteria, which have been recently updated.[7,8] Confirmatory genetic testing is not always required as in some patients who fulfill the criteria a pathogenic variant will not be found and for some disorders like PHACE(S) syndrome or hypomelanosis of Ito, the exact molecular basis is still not identified.[9]

Neurofibromatosis type 1 [NF1 (OMIM 162200)] is the most common NCS, with a prevalence rate of 1:3000 and an incidence rate of 1:2 600 to 1:3 000 live births.[10] It affects female and male equally and every ethnicity. Transmission is autosomal dominant with complete penetrance but variable expressivity, and *de novo* mutations occur in 50% of cases.[11,12] There is loss of expression of the *NF1* gene (chromosome 17q11.2), responsible for the synthesis of neurofibromin, a protein of the Ras/mitogen-activated protein kinase (MAPK) pathway, that intervenes in the regulatory mechanisms of cell proliferation.[13] Germline mutations predispose the whole body to disease whereas somatic mutations will result in mosaic or segmental NF1, which is usually milder.[14] Clinical manifestations are extremely variable between individuals and throughout life and are characterized by multiple *café-au-lait* macules (CALM), axillary and inguinal freckling, and cutaneous neurofibromas. Diagnostic criteria of NF1 were established by the National Institute of Health (NIH) of the United States of America Consensus Conference in 1988 and were last updated in 2021; these criteria are listed on Table 1.[8]

Tuberous sclerosis [TS (OMIM 191100 / 613254)] also known as tuberous sclerosis complex (TSC), is the second most common NCS. It may affect any organ system and is characterized by non-cancerous tumors (hamartomas) developing predominantly in the brain, skin, kidneys, eyes, heart and lungs, causing seizures, intellectual disability, autism, behavioral problems and chronic kidney disease.[15] It has a prevalence rate of 1:20 000 and an estimated incidence of 1:6 000 to 1:10 000 and, similarly to NF1, there is no sex or ethnic differences.[16] The inheritance pattern is autosomal dominant but about two thirds are caused by novel mutations.[15] In around 70% of cases mutations occur in the *TSC2* gene (chromosome 16p13), which encodes for tuberin, and in about 20% of patients in the *TSC1* gene (chromosome 9q34), encoding for hamartin.[17,18] These proteins are heterodimers that act as tumor suppressors by inhibiting the mTOR pathway, involved in cell growth and proliferation.[19] In 10% to 15% of TS patients a pathogenic variant is not identifiable.[7] Several studies have suggested that patients with *TSC2* mutations have more severe phenotypes and, in some patients, a deletion that simultaneously affects the *TSC2* and *PKD1* genes (responsible for autosomal dominant polycystic kidney disease - ADPKD) occurs, leading to contiguous gene syndrome (CGS) TSC2-PKD1.[18,20] The clinical diagnostic criteria for TS were revised between 2018 and 2021 by the International Tuberous Sclerosis Complex Consensus Group and are listed in Table 1.[7]

The increased knowledge concerning the pathophysiology and genetics of NCS over the last two decades has enabled the development of novel promising therapies. Therefore, early diagnosis of NCS is essential, as it allows timely genetic counseling to families, adequate monitoring, anticipatory care, and specific treatment, thus improving the prognosis and quality of life of these patients. A multidisciplinary approach to NCS patients has been advocated, multidisciplinary centers for NCS have grown worldwide, but there is currently no recommended layout or established clinic model with proven efficiency and comprehensive care.

The Multidisciplinary Outpatient Clinic of Neurocutaneous Diseases (MOCND) of Hospital Dona Estefânia – Centro Hospitalar Universitário de Lisboa Central, in Lisbon, Portugal, was created in 2016 due to the growing need of standardization in the care of NCS patients that were previously attending multiple appointments across different specialties with fragmented and heterogeneous follow up and loss of important clinical information. The excessive visits to healthcare institutions, with some involving long travel distances, in addition to other therapies that were routinely needed, resulted in increased school and work absenteeism and high costs. The development of a multidisciplinary clinic, as illustrated in Fig.1, aimed to improve the assessment and management of these complex multiorgan disorders, with the creation of a specialized core team that works in collaboration on the diagnosis and discussion for the optimal care of NCS patients.

The aim of this study was 1) to describe the organization

Table 1 – Updated diagnostic criteria for NF1 and TSC

Revised diagnostic criteria for neurofibromatosis type 1 (NF1), 2021[8]	
A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present: • ≥ 6 *café-au-lait* macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals[a]. • Freckling in the axillary or inguinal region[a]. • ≥ 2 neurofibromas of any type *or* one plexiform neurofibroma. • Optic pathway glioma. • ≥ 2 iris Lisch nodules identified by slit lamp examination or ≥ 2 choroidal abnormalities (CAs) – defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging. • A distinctive osseous lesion such as sphenoid dysplasia[b], anterolateral bowing of the tibia, or pseudarthrosis of a long bone. • A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells. **B:** A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present.	
Revised criteria of TSC, 2021[7]	
Definite TSC: 2 major features or 1 major feature with 2 minor features. **Possible TSC**: either 1 major feature or 2 minor features. **Genetic diagnosis:** A pathogenic variant in TSC1 or TSC2 is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production. Some variants compatible with protein production [e.g., some missense changes] are well established as disease-causing; other variant types should be considered with caution).	
Major criteria	**Minor criteria**
• Hypomelanotic macules (≥ 3; at least 5 mm diameter) • Angiofibroma (≥ 3) or fibrous cephalic plaque • Ungueal fibromas (≥ 2) • Shagreen patch • Multiple retinal hamartomas • Multiple cortical tubers and/or radial migration lines • Subependymal nodule (≥ 2) • Subependymal giant cell astrocytoma • Cardiac rhabdomyoma • Lymphangioleiomyomatosis* • Angiomyolipomas (≥ 2)*	• 'Confetti' skin lesions • Dental enamel pits (≥ 3) • Intraoral fibromas (≥ 2) • Retinal achromic patch • Multiple renal cysts • Nonrenal hamartomas • Sclerotic bone lesions

[a]: If only *café-au-lait* macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (*café-au-lait* macules or freckling) should be bilateral.
[b]: Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.
*: A combination of the 2 major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definitive diagnosis

of the MOCND of our hospital and the evolution in the first five operating years; 2) to share our institutional experience regarding the observed conditions, focusing on the most common: neurofibromatosis type 1 (NF1) and tuberous sclerosis complex (TSC); and 3) to analyze the advantages of a multidisciplinary center and approach in NCS.

METHODS

This study was a retrospective analysis of all patients enrolled in the Multidisciplinary Outpatient Clinic of Neurocutaneous Diseases of Hospital Dona Estefânia - Centro Hospitalar Universitário de Lisboa Central in Lisbon, Portugal, a tertiary pediatric hospital, since its creation in October 2016, until December 2021, comprising a five-year period. Patients from birth to 17 years old inclusive, were included in this clinic from internal referral in our hospital and from external referral of other hospitals with the diagnosis of a NCS or suspected manifestations. A systematic review of all the patients diagnosed with NF1 and TSC regarding clinical information from medical records of each appointment, data on demographics, genetic testing, family history, clinical manifestations, complications, imaging features and therapeutic strategies was carried out. Microsoft® 365 Office Excel, Version 2204 was used for data management and analysis. Descriptive statistics were used presenting data as frequency distribution (frequency and percent), central tendency (mean and median) and range of dispersion. Missing data were deleted, and the results were interpreted in accordance with the total value of existing data.

Confidentiality and data protection were ensured, using a coded and restricted access database authorized only to the authors involved in data collecting and analysis. Written informed consent was obviated due to the characteristics of this casuistic study. The study followed the principles of

ethics and good practice for observational studies, respected the declaration of Helsinki and was approved by the local Ethics Committee.

RESULTS

Institutional experience

Over this period, 281 first appointments were carried out. Of these, 224 (79.7%) patients had identifiable syndromes, with the most frequent disorders being 105 NF1 patients (37.4%) and 35 TSC patients (12.5%). To a lesser extent, our portfolio also included conditions such as hypomelanosis of Ito, Sturge-Weber syndrome, PHACE syndrome (posterior fossa malformations, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities), von Hippel-Lindau syndrome, and other conditions presented in Table 2. The remaining 57 patients had non-specific skin changes not related to a specific syndrome, like *café-au-lait* macules, non-specific pigmentation disorders and melanocytic nevus (not classifiable as epidermal nevus syndromes).

Neurofibromatosis Type 1

Of the 105 children diagnosed with NF1, 52 (49.5%) were female, with a median age of suspicion and referral to the clinic of 12 months (from one month to nine years, mean 2.2 years). At the time of this review, 17 (16.2%) patients had already transitioned to adult care, and one (0.9%) child died from malignant peripheral nerve sheath tumor (MPNST). The group of 87 children still followed in our clinic has to date a median age of 8 years (from seven months to 17 years). The first manifestations, present in all patients (n = 105), were *café-au-lait* macules. Other diagnostic criteria frequently observed were freckling in the axillary or inguinal region (n = 73, 69.5%), neurofibromas (n = 40, 38.1%) with 18 patients (17.1% of total) presenting large plexiform neurofibromas mostly in thoracic, spinal and abdominal locations. Two of these 18 children (1.9% of total) developed malignant peripheral nerve sheath tumor (MPNST). Of the 96 (91.4%) patients that underwent ophthalmological examination, 36 (37.5%) presented Lisch nodules and choroidal anomalies and 22 (22.9%) optic pathway gliomas. The most common neurological findings were learning difficulties and attention deficit/hyperactivity disorder. Other clinical manifestations are listed in Table 3. A mild/moderate phenotype was seen in most patients, with cutaneous, ophthalmological, and mild neurological involvement. Severe phenotypes were classified as patients presented congenital plexiform neurofibromas and severe osteoarticular malformations. A positive family history of NF1 was found in 43 (41.0%), with one or more affected relatives. Genetic testing was performed in 92 (87.6%) patients, and other conditions, namely, multiple sclerosis, Noonan's syndrome and Pfeiffer's syndrome (with genetic confirmation), were also diagnosed in three of those patients''. Comprehensive care of NF1 patients requires multiple specialties, and most patients in our cohort have an average of seven different specialties involved, usually Pediatrics, Neurology, Dermatology, Orthopedics, Ophthalmology, Genetics and Psychology. Presently, 16 patients (15.2%) are receiving treatment with selumetinib for plexiform neurofibromas, in a collaborative work with Instituto Português de Oncologia Francisco Gentil (IPO-FG), in Lisbon.

Table 2 – Portfolio of patients followed in our Multidisciplinary Outpatient Clinic of Neurocutaneus Diseases (MOCND)

Diagnose	**Patients**, n (%)
Neurofibromatosis type 1	105 (37.4%)
Mosaic neurofibromatosis type 1	2 (0.7%)
Neurofibromatosis type 2	4 (1.4%)
Legius syndrome	1 (0.4%)
Noonan syndrome	2 (0.7%)
Tuberous sclerosis complex	35 (12.5%)
Hypomelanosis of Ito	11 (3.9%)
Vascular malformations	22 (7.8%)
Sturge-Weber syndrome	7 (2.5%)
Incontinentia pigmenti	6 (2.1%)
PHACE syndrome*	4 (1.4%)
Ataxia-telangiectasia	3 (1.1%)
von Hippel-Lindau syndrome	3 (1.1%)
Giant congenital melanocytic nevus	2 (0.7%)
Waardenburg syndrome	2 (0.7%)
Bannayan-Riley syndrome	1 (0.4%)
Cafe-au-lait macules	40 (14.3%)
Unespecific pigmentation disorders	17 (6.1%)
Melanocytic nevus**	14 (5.0%)
TOTAL	281 (100%)

*: PHACE: posterior fossa malformations, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities
**: Not classifiable as epidermal nevus syndromes

Tuberous sclerosis complex

During this five-year period, 35 children and adolescents with TSC were assessed in our clinic, 22 of them male (62.9%). At the time of this review, 22 (62.9%) children are still being followed up in our pediatric clinic, with a median age of 13.1 years (from 16 months to 19.6 years). Patients over 18 years old stay on just until adult care is well established, especially in patients with severe cognitive impairment. The characterization of patients and clinical findings is listed in Table 4. Genetic testing was performed in 29 patients (82.9%). Three patients did not undergo genetic testing due to a first-degree relative with known *TSC* mutation (all in *TSC2* gene). The majority of our patients (21, 60.0%)

Table 3 – Characteristics and clinical manifestations of NF1 patients

Characteristics of patients with NF1 (n = 105)	**Patients**, n (%)
Women	52 (49.5)
Performed genetic testing	92 (87.6)
Positive family history	43 (41.0)
NF1 criteria	**n (%)**
≥ 6 *café-au-lait* macules	105 (100)
Freckling in the axillary or inguinal region	73 (69.5)
≥ 2 neurofibromas or 1 plexiform neurofibroma	40 (38.1)
Underwent ophtalmological evaluation	96 (91.4%)
Optic pathway glioma	22 (22.9)*
≥ 2 Lisch nodules or ≥ 2 choroidal abnormalities	36 (37.5)*
Sphenoid dysplasia, Tibial dysplasia or pseudarthrosis[a]	8 (7.6)
Other manifestations	**n (%)**
Neurological	
Developmental delay	9 (8.6%)
Epilepsy	5 (4.8%)
Underwent psychological/cognitive evaluation	78
Learning disabilities	42 (53.8%)**
Attention-deficit/hyperactivity disorder	22 (28.2%)**
Orthopedic	
Scoliosis	29 (27.6%)
Oncologic	
Malignant peripheral nerve sheath tumor	2 (1.9%)
Other tumors	2 (1.9%)

[a]: sphenoid dysplasia (n = 2), tibial dysplasia or pseudarthrosis (n = 6);
*: percentages calculated from patients that underwent ophthalmological examination;
**: percentages calculated from patients that underwent psychological/cognitive evaluation.

showed a pathogenic variant in *TSC2*, rising to 24 (68.6%) if we consider CGS (*TSC2-PKD1*). One patient presented a pathogenic variant only in mosaicism (only in the cells of the affected tissue), resulting from a somatic mutation. Family history was positive in 11 patients (31.4%). All patients fulfilled the 2021 diagnostic criteria, with 16 (45.7%) showing at least five major criteria (maximum 8, minimum 2, median 5 criteria) and 24 (68.6%) manifesting at least one minor criteria, with multiple renal cysts being the most common minor feature found (21, 60.0%). Concerning dermatological manifestations, hypomelanotic macules were observed in all patients, angiofibroma in 21 (60.0%) and Shagreen patch in 13 (37.1%). Neurological manifestations accounted for cortical tubers and subependymal nodules, which were present in all but one patient (probably a mosaic). Three patients (8.6%) had subependymal giant cell astrocytoma (SEGA). Epilepsy occurred in 29 (82.9%), TSC-associated neuropsychiatric disorders (TAND) including intellectual disability (varying from mild to extremely severe) and autism spectrum disorder (ASD), were also very frequent, with 27 (77.1%) patients affected, of which 11 (31.4%) with ASD. Regarding renal and pulmonary manifestations, 18 (51.4%) showed angiomyolipomas and 21 (60.0%) multiple renal cysts; three pubertal patients (8.6%) had lymphangioleiomyomatosis (two of them with concomitant angiomyolipoma) and one showed multifocal micronodular pneumocyte hyperplasia (not associated with lymphangioleiomyomatosis). Four (11.4%) had retinal hamartomas and 17 (48.6%) had a present or previous history of cardiac rhabdomyoma. Inhibitors of the mTOR pathway (everolimus and sirolimus) were started in 14 patients (40.0%) at pediatric age mostly due to renal angiomyolipoma (6/14, 42.9%) and refractory epilepsy (4/14, 28.6%) (Table 4). Patients enrolled for treatment had either a *TSC2* pathogenic variant (10, 71.4%) or CGS (3, 21.4%), with the exception of one patient with no genetic testing that has also started everolimus due to a growing subependymal giant cell astrocytoma (SEGA) located near the Monro foramen with a high risk for intracranial hypertension and refractory epilepsy.

Table 4 – Characteristics, clinical manifestations, and indications for mTOR treatment in TSC patients

Characteristics of patients with TSC (n = 35)	**Patients**, n (%)
Men	22 (62.9)
Performed genetic testing	29 (82.9)
Positive family history	11 (31.4)
Classification	
TSC1	7 (20.0)
TSC2	21 (60.0)[a]
Continuous gene syndrome	3 (8.6)
Genetic testing not performed	4 (11.4)
Unknown result	1 (2.9)
Major criteria	**n (%)**
Hypomelanotic macules	35 (100)
Angiofibroma	21 (60.0)
Ungual fibromas	2 (5.7)
Shagreen patch	13 (37.1)
Multiple retinal hamartomas	4 (11.4)
Multiple cortical tubers and/or radial migration lines	34 (97.1)
Subependymal nodule	34 (97.1)
Subependymal giant cell astrocytoma (SEGA)	3 (8.6)
Cardiac rhabdomyoma	17 (48.6)
Lymphangioleyomiomatosis (LAM)	3 (8.6)
Angiomyolipoma	18 (51.4)
Minor criteria	**n (%)**
'Confetti' skin lesions	1 (2.9)
Dental enamel pits	2 (5.7)
Intraoral fibromas	1 (2.9)
Retinal achromic patch	0
Multiple renal cysts	21 (60.0)
Nonrenal hamartomas	1 (2.9)
Sclerotic bone lesions	3 (8.6)
Other manifestations	**n (%)**
Epilepsy	29 (82.9)
TSC-associated neuropsychiatric disorders (TAND)	27 (77.1)
Intellectual disability	27 (77.1)[b]
Autism spectrum disorder	11 (31.4)
Multifocal micronodular pneumocyte hyperplasia	1 (2.9)
mTOR treatment (n = 14)	**n (%)***
Renal angiomyolipoma	6 (42.9)
Refractory epilepsy	4 (28.6)
Renal angiomyolipoma + refractory epilepsy	1 (7.1)
Subependymal giant cell astrocytoma	1 (7.1)
Subependymal giant cell astrocytoma + refractory epilepsy	1 (7.1)
Other (exuberant skin manifestation)	1 (7.1)
TOTAL	14/35 (40.0)

[a]: Including three patients in which genetic analysis was not performed due to close relative with identified TSC2 mutation
[b]: Mild intellectual disability in three patients.
*: percentages calculated from the total of 14 patients under mTOR inhibitor treatment.

DISCUSSION

Layout of our multidisciplinary clinic and institutional experience

The MOCND initially took place once a month, but with the growing number of patients enrolled it is now held weekly. Patients are always observed simultaneously by a pediatrician and a pediatric neurologist. When needed, patients are referred to other specialties integrating the team, such as Genetics, Nephrology, Ophthalmology, Orthopedics, Neurosurgery, or Dermatology and observed on the same day (Fig. 1). Once a month, the clinic is reserved for TSC patients in collaboration with a pediatric nephrologist. The management of NF1 regarding malignancies, and for patients who meet therapeutic criteria for selumetinib, is shared with IPO-FG in Lisbon.[12,21] When teenagers reach the age of 17, we start the transition process into adult care while maintaining some visits to our clinic until we feel that the patients and their families are well adapted to adult care. Patients that were referred to IPO-FG during adolescence to start selumetinib may transition earlier to adult care in the same institution. Some patients were referred to the clinic by other subspecialties in our hospital and from different

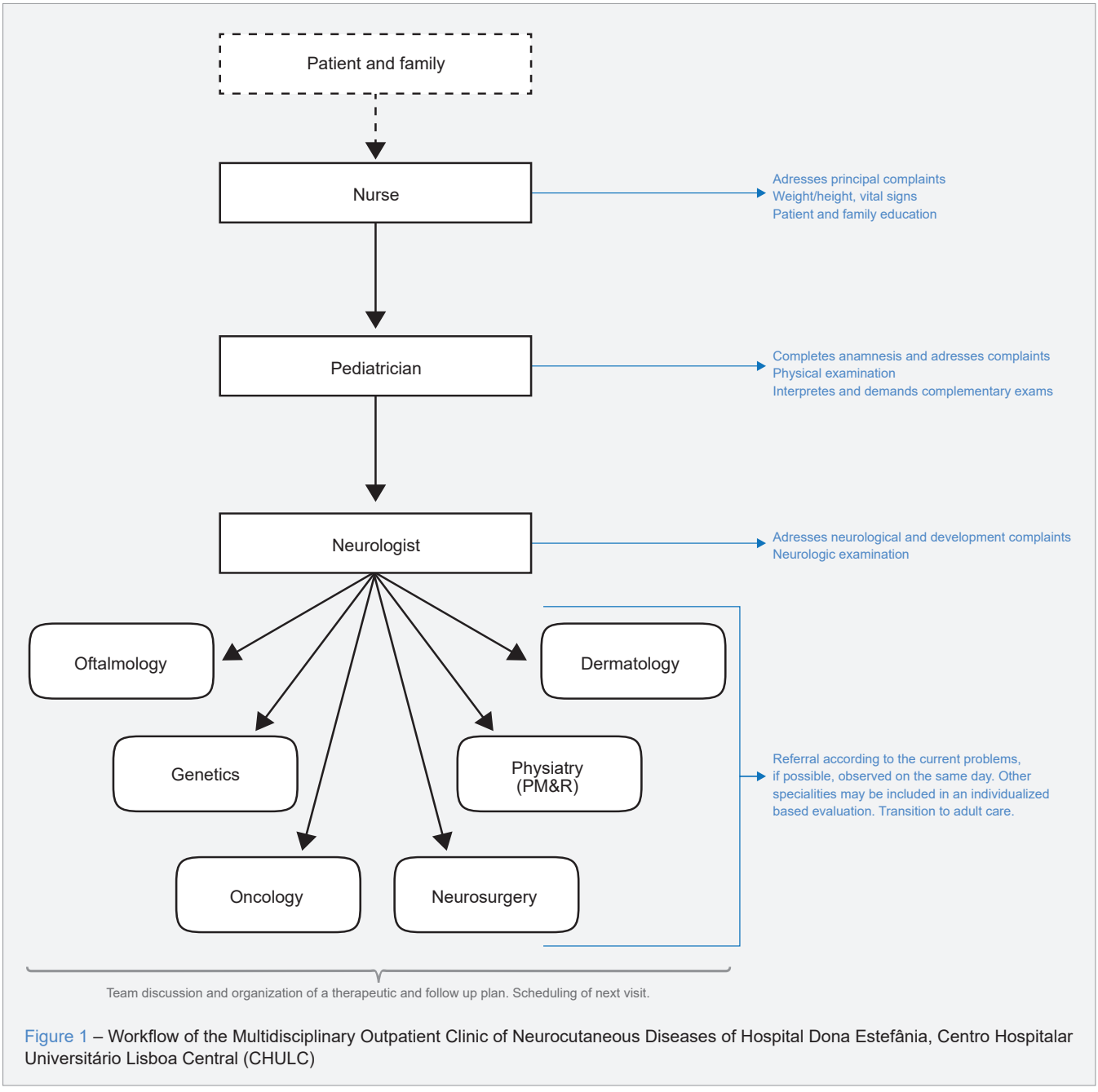

Figure 1 – Workflow of the Multidisciplinary Outpatient Clinic of Neurocutaneous Diseases of Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central (CHULC)

hospitals of the Lisbon metropolitan area, the southern regions of Alentejo and Algarve, and the insular Autonomous Regions of Azores and Madeira Island.

This clinic is innovative in our country and was developed to respond to the need of a more integrated knowledge of these patients, as well as an increasingly reasoned and standardized surveillance and treatment. Multidisciplinary centers for NCS have grown worldwide, Grossen *et al* identified 16 clinics, with very different characteristics adapted to local realities, and only five being exclusively dedicated to pediatric care. The listed clinics were mostly dedicated to neurofibromatosis and in the core team was mainly composed of geneticists and neurologists, and some advocated for a case coordinator.[22-24] In the organization of our clinic, we found great value in congregating diverse neurocutaneous conditions, and we included a pediatrician and neurologist in our core team. Practices such as having close contact with the nurses, supporting patients and families and providing education and information over the disease, as well as follow-up and strategies to deal with challenges in everyday life have also been fruitful.

Therefore, when comparing patients followed before the foundation of the clinic and new patients nowadays, the overall number of appointments is clearly lower, since the average number of NF1 and TSC appointments used to be 17 per year. We believe that the creation of a specialized core team that combines expertise on the diagnosis and the discussion of this chronic multiorgan and potentially life-threatening disease is essential to ensure optimal care and may also be a source of knowledge to propose protocols and guidelines.

Neurofibromatosis type 1

NF1 manifestations appear early in infancy and progress in an age-dependent manner, making early diagnosis difficult, especially in sporadic cases. The revised 2021 diagnostic criteria for NF1 increased diagnostic accuracy in young children. Previously to this change, the diagnostic criteria of the 1988 NIH Conference Consensus would only be met by 54% of patients aged 12 months; around 3% would still miss it at 8 years old..[25] The inclusion of genetic criteria (detection of a pathogenic variant of *NF1* gene) and choroidal anomalies in the ophthalmological examination allow the diagnosis in oligosymptomatic young children without family history.[26] *Café-au-lait* macules are usually the initial manifestation of NF1, detected at birth or early infancy in at least 80% of infants later diagnosed with NF1.[8,12,13] The presence of six or more CALM greatly increases the likelihood of NF1 diagnosis.[26] The number and size increase over time, and in our cohort, in accordance to similar reports, it was the main reason of referral to the clinic, contributing strongly to the diagnosis at a median age of 12 months. Another reason for referral was screening due to a positive family history. Genetic testing was performed in 92 patients (87.6%), a higher rate when compared to other series, which is justified by the young age of most patients (under 5 years old), who did not yet fulfill clinical criteria and had parents in reproductive age. Moreover, all complex patients undergo genetic testing before starting therapy with selumetinib.

Most of the children followed in our clinic have a mild to moderate phenotype. Severe phenotypes are generally seen in patients with congenital plexiform neurofibromas and severe osteoarticular conditions. In our series, only one boy had sphenoid wing dysplasia, and another child presented tibial dysplasia detected in the first month of life, prompting immediate referral to our clinic, and plexiform neurofibromas were detected in 18 patients (17.1%). Neurofibromas are benign tumors of atypical Schwann cells, fibroblasts and mast cells. They are classified as cutaneous (which are present in up to 99% of adult NF1 patients), subcutaneous and plexiform (diffuse and nodular).[27] Numerous neurofibromas are the main cause of morbidity causing aesthetic changes with significant disfigurement and discomfort. Diffuse plexiform neurofibromas are congenital lesions, located superficially or internally, that involve multiple fascicles and nerve branches. The prevalence rate of superficial plexiform neurofibromas in NF1 is reported to be around 30%, reaching 50% when accounting also for internal neurofibromas. Growth is unpredictable, with studies suggesting bursts during adolescence. It is the major cause of pain, deformity, mass effect and functional neurological impairment, and has an increased risk of malignant transformation to MPNST.[21,28]

Malignant peripheral nerve sheath tumors develop during the first decade of life, in pre-existing plexiform neurofibromas, and are aggressive and potentially fatal. Even though authors suggest screening for MPNST through magnetic resonance imaging (MRI), this is not always an accessible test and the long risk period for appearance and variable locations make this difficult. If available, F-fluorodeoxy-glucose (FDG)-positron emission tomography (PET) may be useful to distinguish between benign and malignant tumors in these patients. Furthermore, it is essential to identify early clinical manifestations suggestive of malignant transformation, such as rapid increase in size of a pre-existing or 'new' neurofibroma, pain and changes in appearance or new neurological signs.[27]

Optic pathway glioma is the most common CNS tumor in NF1, with an incidence rate of 15%.[29] It usually appears before the age of six and can be located anywhere along the optic pathway, but most frequently develops in the anterior visual tract and is unilateral. Histologically, it is usually a low grade pilocytic astrocytoma and does not progress

or metastasize, even though other types are possible. In our cohort, similarly to other series, around 20% of children were diagnosed with optic pathway glioma.[27,29–31] These patients need regular neuroimaging surveillance, coordinated by pediatric neurologist, neuro-oncologist and ophthalmologist. In our series, only one required chemotherapy due to the size of the tumor, and the other, underwent surgical removal.

Neurological complications of NF1 are frequent and include cognitive impairment, learning disabilities, autism spectrum disorders, other CNS tumors, epilepsy, seizures, headaches and hydrocephalus.[32] We found learning difficulties and attention deficit/hyperactivity disorder in around half of the patients, similarly to other series.[33]

Tuberous sclerosis complex

In the group of patients with TSC, we found a positive family history in about one third (n = 11), in close accordance with the literature.[19] Nevertheless, we performed genetic testing in most of our patients (29/35, 82.9%). Molecular confirmation was obviated in three patients that fulfilled clinical criteria and had a first degree relative with a causal *TSC2* variant identified, assuming the same mutation was to be found. One patient abandoned follow-up in our hospital, one did not perform genetic testing at time of diagnosis and already transitioned to adult care, and another missed the genetics appointments. One patient performed genetic testing in another country and parents lost the result. Most of our patients (n = 21; 60.0%) showed a *TSC2* mutation, accounting for 68.6% when CGS is considered (a deletion that simultaneously affects *TSC2* and *PKD1* genes), similar to other TSC studies.[17,18] As for NF1, the high percentage of genetic testing performed in TSC was mostly justified for genetic counseling purposes.

Regarding clinical manifestations, hypomelanocytic macules were observed in all our patients. This manifestation occurs in about 90% of TSC patients and is present at birth or during early infancy.[16] The percentages of patients with angiofibroma and Shagreen patch (skin coloured oval-shaped connective-tissue *naevi*) were also similar of those from other reports.[15] 'Confetti' skin lesions (1 to 3 mm hypopigmented macules usually scattered on the limbs) are more frequently reported in adult series, with studies in children reporting a 3% frequency, which is in agreement with this cohort.[16] The incidence rate of neurological complications such as epilepsy and TAND were frequent, specially autism spectrum disease, in line with the literature, and with substantial impact on the quality of life of the child and the family.[16] Three patients presented with SEGA, and they are all under treatment with mTOR pathway inhibitors. The smaller number of patients with renal angiomyolipomas and retinal hamartomas, are probably related to a later age of apperance.[34–36] Of notice, we listed three patients with lymphangioleiomyomatosis, all of them adolescent males. This was a surprising finding, as this manifestation is usually described in female patients after the third decade of life, due to the influence of estrogen production.[37,38]

Treatment of TSC with mTOR inhibitors in children, such as everolimus and sirolimus, is formally indicated in symptomatic SEGA without indication for surgery and refractory epilepsy, and may also be considered, according to England's National Health Service, in children over three years old and adults with TSC-associated angiomyolipoma over 30 mm which demonstrates internal growth.[39–41] Fourteen patients started mTOR inhibitors (13 everolimus, one sirolimus). One patient started treatment for a non-formal indication, by having very exuberant dermatological manifestations, with serious impact on self-esteem. Furthermore, several studies have demonstrated dermatological improvement in patients receiving treatment with everolimus.[41] All our patients treated with mTOR inhibitors have *TSC2* mutation/CGS which suggests that this type has greater severity compared with *TSC1*.[18]

The results concerning clinical efficacy, outcomes, and adverse effects of treatment of our cohort with mTOR inhibitors will be published separately.

Final remarks

The organization and development of a multidisciplinary clinic in our hospital has been of great value for both patients and their families as well as for the professionals who work with them.

For patients, the main advantages are:

- The convenience of seeing a multitude of specialists in one single clinic visit, reducing the number of visits to the hospital, saving time and money.
- More systematic surveillance (in terms of clinical parameters and tests performed).
- In cases that fulfill criteria for specific treatments, the possibility of earlier initiation.
- Having an assigned physician, namely the coordinator of the core team, as an interface to the healthcare system, who promotes better compliance with the proposed treatments and follow up and helps to address the diverse problems and doubts of patients and their families.
- Better and more effective pediatric-to-adult transition care.
- Increased quality of care.
- Making connections between patients and families for support and sharing difficulties.

For healthcare professionals, the main gains are:

- Easier compilation and better organization of

information on each patient.
- Increased comprehensive knowledge about the diseases.
- Greater experience in the follow-up and treatment of each patient (due to the consistency of the core team in each appointment).
- Multidisciplinary open discussions.
- Possibility of developing diagnostic, follow-up, and therapeutic protocols.
- Greater ease in discussing difficult cases with international centers.
- Participation in studies and clinical trials of new treatments.

This is, however, a demanding task, requiring detailed preparation for each appointment, logistics and coordination of the agendas of the different specialists.

We hope, therefore, that our experience may be useful to serve as a model for the creation of other multidisciplinary teams, to promote earlier patient referral to our clinic and to inspire adult care to replicate the model, facilitating this transition and maintaining its benefit for patients.

CONCLUSION

Neurocutaneous diseases are a heterogeneous and complex group of conditions. Clinical manifestations are very diverse and evolve throughout the patient's life, with significant morbidity. It is essential to promote a systematic and multidisciplinary approach to promptly diagnose complications, to provide the best treatment and contribute to the improvement of the overall health and quality of life of children and adolescents with NCS, as well as their families. Multidisciplinary clinics have shown to improve patient satisfaction and outcomes.

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AUTHOR CONTRIBUTIONS

AIC, TF: Data acquisition and analysis, literature review, draft of the paper.

MR: Data analysis, review of literature, draft of the paper.

AP, RP, AI, MA, MJPL, RLS: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

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