Review

Systematic Review of the Dysembryoplastic Neuroepithelial Tumor Characteristics

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Abstract

Objective: To gather the descriptions of dysembryoplastic neuroepithelial tumor (DNT) characteristics described in the literature. **Method**: Systematic review of the clinical characteristics and evolution of DNT, topographic diagnosis, neuroimaging, anatomical and pathological findings and surgical response. The search was made in the Medline and Lilacs systems from 1988 until December 2005. Results: Found were 218 articles with115 selected to include the characteristics being investigated. Records of 952 patients with DNT were found from 115 articles, of which 446 (57.0%) were men. The minimum age ranged from 8 months to 75 years (average 14.2 years) and maximum age of 2 to 75 years (average 29.6 years). The average minimum age of epilepsy onset was 98.5 months (minimum 1 month; maximum 610 months). The average maximum age of epilepsy onset was 246.6 months (minimum 1 month; maximum 726 months). Epileptic seizures occurred in 96.4% and all fulfilled the criteria for drug-resistance. The neuroimaging showed the absence of peritumoral edema in 97.2% and lack of mass effect in 90.4%. The most frequent histopathologic finding was cellular heterogeneity with the presence of oligodendrocyte-like cells in 65.5%; nonspecific form occurring in 12.6%. **Conclusion**: DNT is a tumor that affects with similar proportion between men and women, mainly in young adults until the third decade of life, with epileptic seizures the main initial manifestations. Mass effect is not presented and oligodendrocyte-like cells are the most frequent findings.

Keywords: Dysembryoplastic neuroepithelial tumor; DNT; Daumas-Duport C.

Introduction

The dysembryoplastic neuroepithelial tumor (DNT) was described by Catherine Daumas-Duport in 1988, defining and characterizing its several histopathologic forms. Daumas-Duport showed that DNT is a stable tumor, of benign behavior, supratentorial cortical preferred location, mainly in the temporal lobe, frequently involving mesial structures. In the original description, attention was called to the difficult differentiation between DNT and the histopathologic characteristics of low-grade and high-grade gliomas.[1] In 1999, Daumas-Duport described the nonspecific form in which the specific glioneural element is not identified. In those cases, the tumor presented specific radiological and clinical characteristics; criteria that associates the histopathologic result to the differences of pylocitic astrocytomas, oligodendrogliomas or oligoastrocytomas.[2-3] The diagnosis of DNT should be considered utilizing clinical criteria and neuroimaging, especially when the presence joins the four fundamental criteria for the diagnosis of the disease:[2] (1) focal epilepsies with or without secondary generalization, usually initiating before 20 years of age; (2) absence of progressive neurological deficit; (3) supratentorial lesion with topography, mainly cortical, best demonstrated

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in magnetic resonance; (4) absence of mass effect in computerized tomography or magnetic resonance, and absence of cerebral edema. Most of the time, drug-resistant epilepsy is cured after its total surgical removal, which additionally prevents hemorrhages and intra-timorous infarcts. The patients with complete or incomplete surgical removal of the tumor do not present evidence of clinical or radiological recurrence in long-term follow-up.[4-6] The objective of this revision is to contribute with the synthesis of registrations in cases of described DNT, in the joint analysis of their demographic characteristics, of epileptic, clinical, neuroimaging and histopathologic semiology, calling attention to the importance of DNT in the differential diagnosis of CNS tumors.

Method

A systematic revision of the literature was done through research in Medline and Lilacs databases. Used were keywords dysembryoplastic neuroepithelial tumor, DNT and Daumas-Duport C. Revision studies, case reports and longitudinal studies were selected in the Portuguese, Spanish, English and French languages. Studied were articles published between 1988 and December 2005. Statistical study with univariate analysis was done using the program Epi info, version 6.04, January 2001.

Results

Found were 115 articles with case descriptions of patients with DNT diagnosis. The total number of patients studied in the 115 articles was 952. The country with the greatest frequency of articles was Japan (n=21, 18.3%), followed by France and the United States (n=16, 13.9% each) and finally Germany and the United Kingdom (n=10, 8.7%) (Tables 1 and 2).

A progressive increase in the frequency of case registrations is observed of published article distribution since 1988, when DNT was first described (Figure 1).

In 782 patients where the gender was registered, 336 (43%) were female and 446 (57%) were male. Those patients whose cases were described in more than one article were considered in only one, avoiding duplication of information. The average age of the cases at the moment of DNT diagnosis varied from 8 months to 75 years, having the average values of 14.2 years for the minimum age and 29.6 years for the maximum age of each series.

Table 1 – Article relationship of DNT patient series published in the literature during the period 1988 to December 1999

Author	Year of Publication	Number of Cases
Daumas-Duport[1]	1988	39
Prayson[7,8]	1992/1993	3
Koeller[9]	1992	6
Kirkpatrick[10]	1993	27
Vali[11]	1993	4
Gottschalk[12]	1993	1
Daumas-Duport[13]	1993	14
Sato[14]	1993	1
Wolf[15]	1993	6
Hirose[16]	1994	1
Kuroiwa[17]	1994	3
Raymond[18]	1994	16
Leung[19]	1994	2
Kuchelmeister[20]	1995	1
Iwanaga[21]	1995	1
Lellouch-Tubiana[22]	1995	2
Taratuto[23]	1995	14
Abe[24]	1995	3
Wolf[25]	1995	11
Raymond[26]	1995	21
Kuroiwa[27]	1995	10
Kordek[28]	1996	2
Prayson[29]	1996	11
Ostertun[30]	1996	16
Kimura[31]	1996	1
Lemest[32]	1996	5
Ausman[33]	1996	1
Kasturi[34]	1996	1
Weissman[35]	1996	1
Itoh[36]	1997	2
Radhakrishnan[37]	1997	1
Devaux[38]	1997	7
Shimbo[39]	1997	1
Cervera Pierot[40]	1997	4
Lanzieri[41]	1997	1
Torres[42]	1997	1
Romeike[43]	1998	1
Hirose[44]	1998	1
Tanigushi[45]	1998	1
Rosemberg[46]	1998	11
Tatke[5]	1998	1
Yasha[47]	1998	1
Andermann[48]	1999	1
Prayson[49]	1999	1
Honavar[50]	1999	74
Asano[51]	1999	1
Daumas-Duport[2]	1999	40
Thom[52]	1999	5
Kaplan[53]	1999	5
Radhakrishnan[54]	1999	1
Fomekong[55]	1999	16
Guesmi[56]	1999	8
Wierzba-Bobrowicz[57]	1999	1
Kordek[58]	1999	6
Whittle[59]	1999	1

Patient neurological exam was normal in 507 (89.1%) cases with DNT and altered in 62 (10.9%) of the cases where exam was done. Electroencephalogram was done in 192 patients; normal in 30 (15.6%) patients

Table 2 – Article relationship of DNT patient series published in the literature during the period 2000 to December 2005

Author	Year of Publication	Number of Cases
Gyure[60]	2000	11
Prayson[61]	2000	18
Hammond[62]	2000	1
Elizabeth[63]	2000	1
Reis[64]	2000	6
Pan[65]	2000	1
Fujimoto[66]	2000	1
Nakatsuka[67]	2000	1
Lee[68]	2000	20
Hennessy[69]	2001	10
Jorge[6]	2000	2
Hodozuka[70]	2000	4
Aronica[71]	2001	13
Baisden[72]	2001	10
Argyropoulou[73]	2001	1
Adamek[74]	2001	1
Richardson[75]	2001	5
Tatke[76]	2001	10
Sisodiya[77]	2002	8
Sztriha[78]	2002	1
Kameyama[79]	2001	5
Valenti[80]	2002	9
Stanescu Cosson[81]	2001	53
Komori[82]	2002	11
Quarato[83]	2002	1
Pasquier[84]	2002	61
Schramm[85]	2002	1
Shin[86]	2002	3
Prayson[87]	2002	14
Degen[88]	2002	21
Fujisawa[89]	2002	3
Kurtkaya-Yapicier[90]	2002	1
Hamada[91]	2003	1
Brami-Zylberberg[92]	2003	1
Fernandez[93]	2003	14
Vaquero[94]	2003	7
Rushing[95]	2003	1
Park[96]	2003	17
Seo[97]	2003	9
Onguru[98]	2003	1
Karatas[99]	2003	1
Maehara[100]	2004	4
Hasselblatt[101]	2004	2
Litrico[102]	2004	1
Escosa-Bage[103]	2004	1
Nolan[104]	2004	26
Labate[105]	2004	16
Vogelgesang[106]	2004	14
Neder[107]	2004	10
Cataltepe[108]	2005	14
Giulioni[109]	2005	4
Aronica[110]	2005	17
Sakuta[111]	2005	26
Hall[112]	2005	1
Wang[113]	2005	1
Krossnes[114]	2005	1
Specchio[115]	2005	1
Takahashi[116]	2005	24
Rosenberg[117]	2005	11
Jensen[118]	2005	1

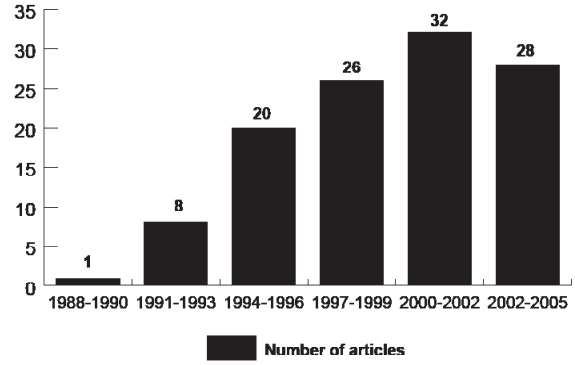

Figure 1 – Number of DNT case series articles published each three years since the original description in 1988

and altered in 162 (84.4%). Supratentorial location occurred in 923 (97.9%) cases and infratentorial in 20 (2.1%) (Table 3).

Intracranial pressure was the compromising characteristic highlighted in most of the studies. Mass effect was not found in 350 (90.4%) cases, present in 37 (9.6%) cases, while the data was not available in the others. Peritumoral edema was not identified in 377 (97.2%) cases, identified in 11 (2.8%) cases, while the data was not available in the others. Tumorous calcification was observed in 75 (17.6%) cases, while found absent in 351 (82.4%) cases where that description was available. In 107 (24.4%) cases was contrast enhancement, while this did not occur in 328 (75.6%) cases. Calvaria deformity occurred in 64 (16.5%) cases and was absent in 325 (83.5%) cases; data not shown. SPECT was abnormal in 44 (83.6%) cases, normal in 9 (16.4%) cases and data was not available in 883 cases. The tumor presented intracortical location in 609 (88.0%) registrations and subcortical presentation in 83 (12.0%) cases. The registration of surgical procedure was clearly described in 713 cases. Total resection was done in 536 (75.2%) cases and partial resection in 177 (24.8%) cases. Continuation of postsurgical follow-up showed control of the recurring epileptic crises, with the period varying from 2 to 348 months, with an average of 65.3 months.

Specific histopathologic findings of DNT were described in most of the studies, with presence of multinodal architecture in 542 (56.9%) cases, specific glioneural element in 338 (35.5%) cases and cellular heterogeneity and oligodendrocyte-like cells in 623 (65,4%) cases. Cortical dysplasia was present in 273 (28.7%) cases. Nonspecific form of DNT was described in 120 (12.6%) cases (Table 4).

Table 3 - Location of DNT considering supra- and infra- tentorial topographies

Location	Supratentorial (923)	Infratentorial (20)
Temporal	625	–
Frontal	137	–
Parietal	59	–
Occipital	28	–
Insular	3	–
Temporal-parietal	9	–
Temporal-occipital	9	–
Temporal-parietal-occipital	3	–
Temporal-frontal	2	–
Temporal-insular	5	–
Parietal-occipital	10	–
Frontal-temporal-parietal	2	–
Frontal-parietal	2	–
Central	9	–
Centrotemporal	2	–
Trigonoseptal	1	–
Septum pellucidum	11	–
Lateral ventricle	1	–
Caudate nucleus	5	–
Cerebellum	–	6
Fourth ventricle	–	11
Brainstem	–	3

The presence of drug-resistant epileptic crisis was registered in most of the cases, a total of 854 (96.4%), absent in 32 (3.6%) cases and with no data given in 66 cases. The minimum age of epileptic crises onset varied from 1 to 610 months with an average of 98.5 months and the maximum age of epileptic crises onset varied from 1 to 726 months with an average of 246.6 months. Nineteen cases were submitted to radiotherapy; two cases to chemotherapy.

Table 4 - Histopathologic characteristics of DNT

Histopathologic characteristics of DNT	Number of cases (%)
Multinodal architecture	542 (56.9%)
Specific glioneural element	338 (35.5%)
Cellular heterogeneity - oligodendrocyte-like cells	623 (65.4%)
Cortical dysplasia	273 (28.7%)

Discussion

The dysembryoplastic neuroepithelial *tumor* (DNT) was described 19 years ago by Daumas-Duport, a French pathologist interested in the clinical observation and findings of MRI in patients with drug-resistant temporal epilepsy submitted to surgery that received the diagnosis of low grade glioma. Daumas-Duport identified 39 cases that, although similar to low-grade glioma, presented suggestive characteristics of a dysembryoplastic origin, especially with the presence of cortical dysplasia and of multiple lineages of cells with astrocytic and oligodendrocytic neuronal components. Associate to those descriptions, the revision of the neuroimaging exams and the clinical evolution stood out, for they presented a lack of mass effect or peritumoral edema, high epileptogenic frequency and invariably benign postoperative behavior, where all the patients presented control of the crises, independent of total resection.[119] The perspicacity and the power of observation of that pathologist, leaving the slides and departing for the clinical correlation and neuroimaging of the findings allowed the description of DNT through revision of patients records to those submitted to epilepsy surgery in two separate centers, Hospital Sant Anne-Paris, France and Mayo Clinic-USA. For the first time in the history of pathology, clinical parameters and neuroimaging were part of the diagnostic criteria of a brain tumor.

Prayson and Ester, in a 1992 publication, postulated DNT to be a hamartomatous lesion formed by a disorganized arrangement of glial elements and cytologicaly normal neuronals and not a separate entity, in which the association with cortical dysplasia and the presence of multiple cellular lineages leads to a dysembryoplastic origin. On the other hand, excessive cellular proliferation and the formation of a mass type lesion suggests a neoplastic process, albeit benign.[7,120]

Histopathologic appearance and benign course suggests that DNT is actually a cortical development malformation and not a neoplastic lesion. The presence of cortical dysplasia focus is strongly suggestive that DNT has its beginning during the formation of the cortex.[3,121]

The clinical course seemingly indolent of DNT hinders and makes vital the importance of the differential diagnosis with other tumors of poor prognosis. The main tumors involved in the differential diagnosis of DNT, especially for the pattern of cellular heterogeneity, are mixed oligoastrocytoma and ganglioglioma.[122]

In the histopathologic point of view, DNT

can be distinct from gangliogliomas for its multinodal architecture, myxoid matrix and predominance of oligodendrocyte-like cellular population. The typical multinodal pattern and the presence of cortical dysplasia are particularly important characteristics, especially when typical cytological findings of DNT are not clearly observed, hindering the histopathologic diagnosis. In DNT there is a lack of bizarre neurons and of gigantic ganglion-like cells, an abundance of estromal connective tissue and lymphocytic perivascular infiltration, which are frequently found in gangliogliomas. Gangliogliomas are not intracortical tumors but are placed at random in this area.[123-125] The differentiation of DNT and of ganglioglioma by histopathologic characteristics and neuroimaging isolated is not possible.[126] This differential diagnosis has a great therapeutic importance because a distinct biological behavior is presented; radiotherapy indicated in gangliogliomas is never indicated in DNT. There are reports of transitional forms between DNT and ganglioglioma. On the other hand, the misinterpretated diagnosis of DNT with oligoastrocytoma should be avoided, therefore, the loss of the specific glioneural element in pathology samples badly prepared lead to grave mistakes in the conduction of treatment to individuals, who end up being submitted to such addictive therapies as radiotherapy and chemotherapy in an unnecessary manner.[69] Isolated reports in the literature of malignant transformation of DNT, as well as that described by Hammond and cols, in 2000, and by Rushing and cols, in 2003, reinforce the importance of long-term follow-up in atypical cases of DNT. [62,95] Tumor induction in CNS and the malignant transformation of an initially low-grade tumor are adverse effects well recognized of radiotherapy. The precise mechanism of correlation of radiation with oncogenesis is not well identified. Therefore, the precise diagnosis of DNT avoids treatments with radiotherapy and their serious consequences.

Clinical and neuroimaging contribution in the diagnosis of DNT was fundamental when Daumas-Duport noticed that a great part of the diagnoses could not have been done solely with pathology separately. The clinical presentation of DNT is stereotyped, characterized by the long history of drug-resistant epilepsy and the absence of progressive neurological deficit in individuals; a majority youths. Epilepsy is the clinical form most common in the presentation of DNT, present in an overwhelming majority of the cases, especially when the tumor has typical supratentorial presentation.[127]

Related in the literature, although merely once, was the family history of DNT, demonstrating the importance of genetic studies involving patients with this pathology.[101]

The great number of patients related in the compared literature today allows to clearly establish the clinical and evolutionary characteristics of this tumor. The importance of the differential diagnosis between DNT and other tumors, through the confident histological identification of DNT, when possible solely by histopathologic sample and the correct evaluation of clinical criteria and neuroimaging for the diagnosis of DNT, allow a great number of young individuals to be correctly identified as DNT carriers. Surgery could be considered as an optimal treatment option in those patients with drug-resistant epilepsy, avoiding aggressive, unnecessary treatments, such as radiotherapy and chemotherapy.

Our systematic revision gathering the characteristics of 952 patients related in 115 scientific articles can contribute to this multidisciplined vision that, although thoroughly recognized, had never been approached with such an expressive group of patients. Our results reinforce that DNT is an intracranial tumor whose diagnostic criteria include: young individuals with drug-resistant epileptic seizures; without important neurological deficit and with neuroimaging exam showing tumorous lesion without edema, mass effect, or contrast reception. The postoperative of most patients showed that the epileptic seizures are controlled, even in the cases with incomplete resection, and that the patients evolved without neurological deficit.

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