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Clinical Research

The Costs of Childhood Epilepsy in Italy: Comparative Findings from Three Health Care Settings

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Summary: *Purpose:* To determine the direct costs of epilepsy in a child neurology referral population, stratified by disease, duration, and severity, comparing three different health care settings [i.e., teaching or clinical research (CR) hospitals, general hospitals, and outpatient services].

Methods: Patients were accepted if they had confirmed epilepsy and were resident in the center catchment area. Eligible subjects were grouped in the following categories: (a) newly diagnosed patients; (b) patients with epilepsy in remission; (c) patients with active non–drug-resistant epilepsy; and (d) those with drug-resistant epilepsy. Over a 12-month period, data regarding the consuming of all resources (i.e., consultations, tests, hospital admissions, drugs), were collected for each patient. Using the Italian National Health Service tariffs, the unit cost of each resource was calculated and indicated in Euros, the European currency.

Results: A total of 189 patients was enrolled by two teaching-CR hospitals, two general hospitals, and two outpatient services. The patients were evenly distributed across the four categories of epilepsy. The mean annual cost per person with epilepsy was 1,767 Euros. Drug-resistant epilepsy was the most expensive category (3,268 Euros) followed by newly diagnosed epilepsy (1,907 Euros), active non–drug-resistant epilepsy (1,112 Euros), and epilepsy in remission (844 Euros). Costs were generally highest in teaching-CR hospitals and lowest in outpatient services. Hospital services were the major cost in all epilepsy groups, followed by drugs.

Conclusions: The cost of epilepsy in children and adolescents in Italy tends to vary significantly depending on the severity and duration of the disease Hospitals services and drugs are the major sources of costs. The setting of health care plays a significant role in the variation of the costs, even for patients in the same category of epilepsy. **Key Words:** Quality of care—Direct costs—Epilepsy—Children.

In recent years, the economic assessment of a chronic disease has become of paramount importance because, given the limited resources assigned to the health care services, a more rational allocation of the available funds is increasingly required. For this reason, the burden of the disease must be defined in terms of the number of affected individuals and spectrum of severity. Epilepsy is a common clinical condition with an annual incidence in Western countries of 30–50 cases per 100,000 and a prevalence of five to eight cases per 1,000 population (1), with different characteristics in children and adults and a variable degree of response to the available treatments. On this basis, one might expect different costs for the management of epilepsy, depending both on some demographic and on specific clinical features of the disease.

Several cost studies have been published in epilepsy (2), which cannot be compared because of the different methodologic approaches. They refer specifically to the study populations, methods of investigation, and selection of the costs included. In addition, the economic burden of epilepsy may reflect the quality of care as well as national and local attitudes in the health care organization. Data on children and adolescents is scarce despite

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the frequency and relevant features of epilepsy in this age group.

For these reasons, we carried out an economic survey in Italy to assess the costs of epilepsy in a child neurology referral population. We compared three different health care settings [i.e., teaching and clinical research (CR) hospitals, general hospitals, and outpatient services].

PATIENTS AND METHODS

The study population included children, adolescents, and a few young adults followed up by child neurologists working at three different institutions: (a) a university department (or CR hospital), where the equipment and the resources available facilitate the best management of epilepsy; (b) a general hospital, where the necessary steps for the management of the patient can be accomplished by an epileptologist, without access to sophisticated technology and dedicated staff (as present in a); and (c) an outpatient department where children with epilepsy are seen by a child neurologist, but with no access to hospital beds and without specific resources for epilepsy patients.

The inclusion of some young adults with epilepsy in our sample reflects the desire of some patients and their families to continue being treated by the same physician. Patients were included in the study if their epilepsy fulfilled a standard diagnostic definition (i.e., repeated unprovoked seizures 24 h apart) (3). Patients with an isolated seizure were included if they had clinical and EEG evidence of a specific type of epilepsy or magnetic resonance imaging (MRI) evidence of an epileptogenic brain lesion. Epileptic seizures were defined according to the Classification of the International League Against Epilepsy (4). To be accepted, a patient had to be resident within the catchment area of the participating institution. The requirement reflected the need to minimize selection bias among this referral population. Eligible patients were then grouped into the following categories, with specific reference to the duration and severity of the disease: (a) newly diagnosed patients (i.e., patients whose diagnosis was first made or confirmed at the participating institution; (b) patients with epilepsy in remission (i.e., patients with complete seizure control in the 12 months before admission; (c) patients with active non–drug-resistant epilepsy (i.e., with seizures judged by their own physician to be non–drug resistant; and (d) patients with drug-resistant epilepsy (i.e., patients with seizures in the preceding 2 years, judged by their physicians to be drug resistant).

At enrollment, each individual's physician recorded all relevant demographic and clinical data, including the presence of any disabilities and any specific requirements regarding schooling, such as special support and rehabilitation. In each eligible patient, epilepsy was defined with reference to seizure type and frequency, etiology, and syndromic pattern (5). Treatment at entry was also indicated with reference to the number and type of drugs. Over a 12-month period, patients or their parents at each follow-up appointment reported data regarding seizure frequency, laboratory and diagnostic tests, outpatient evaluations, and hospital admissions in an ad hoc diary.

All the data were recorded by the physicians in attendance into a semistructured questionnaire. Seizures, laboratory and diagnostic tests, outpatient evaluations, and hospital admissions were itemized therein, and if any was reported one or more times, it was numbered on a checklist. Day hospitals were recorded separately from other hospital admissions, for which the length of stay was also noted. To assess the cumulative/total quantity (in milligrams), of drugs consumed over the study period, all treatments and treatment changes were recorded, and the figures acquired then constituted the basis of the preliminary drug treatment cost assessment. This data were then transferred into a common database and analyzed separately for each epilepsy category and institution. We produced estimates of direct costs associated with epilepsy from the Italian National Health Service (INHS) perspective. Any costs relating to specialist consultations and laboratory and instrumental tests were estimated by applying the INHS tariffs. Hospital costs were estimated using tariffs from the system (similar to DRGs) that was recently introduced in Italy. Drug costs were calculated by multiplying the daily dosage by the public price. The total costs of diagnosis and treatment were calculated by multiplying each resource consumed (consultations, tests, hospital admissions, drugs) by its unit cost, which was identified in the same way as previously described. The monetary values were indicated with reference to the national cost parameters and were then converted into Euros (the European currency, which is almost equivalent to the U.S. dollar).

Data analysis was achieved by applying two separate strategies: (a) comparing the different epilepsy groups after pooling the data from the three institutions; and (b) comparing the data reported by the three institutions on the same epilepsy group. Student's t test, analysis of variance, and χ^2 for heterogeneity or trend were used where appropriate.

RESULTS

During the period from October 1996 through June 1998, 189 patients were enrolled by two teaching-CR hospital departments [Pisa and Pavia, total 74 (39%)], two general hospitals [Alessandria and Reggio Emilia, total 63 (33%)], and two outpatient services [Bergamo and Grosseto, total 52 (28%)].

The sample included 96 boys and 93 girls aged 4 months to 21 years (mean, 8.8 years). There were 63 newly diagnosed patients, 63 patients with epilepsy in remission, 21 patients with active non–drug-resistant epilepsy, and 42 patients with drug-resistant epilepsy. The sex ratio was fairly similar across epilepsy groups (Table 1). The sample included mostly patients aged 5–14 years, with mild intergroup variations. Newly diagnosed patients were the youngest (mean, 6.6 years), and patients in remission were the oldest age group (mean, 10.3 years). Schooling assistance ranged from 1.6% of newly diagnosed patients to 59.5% of patients with drug-resistant seizures. Likewise, disability (any type) was present in 3.2% of newly diagnosed patients and in 64.3% of those with drug-resistant seizures. The corresponding percentages for physical therapy were 6.3% and 54.8% (Table 1). Partial and generalized epilepsies were equally distributed throughout the entire study population (Table 1), with mild differences across epilepsy groups, except for patients with non–drug-resistant seizures (partial epilepsies, 66.7%). The rate of detection of a specific etiology for epilepsy ranged from 11% in newly diagnosed patients to 55% in drug-resistant patients and tended to be increasingly more frequent with disease severity and response to treatment. A similar trend was present for concurrent illnesses. Duration of epilepsy was <3 years in almost all the newly diagnosed patients and >6 years in 19% of patients with non–drug-resistant seizures and in up to 52.4% of those with drug-resistant seizures. Twenty-one percent of newly diagnosed patients had an isolated seizure, and 19% had daily seizures. Among drug-resistant cases, 83% had more than one seizure per month. Thirty-two percent of patients with newly diagnosed epilepsy were untreated, and 9% received polytherapy. The proportion of cases receiving two drugs or more was slightly higher among those patients who were in remission (22%) compared with those with non–drug-resistant seizures (14%), but it was as high as 81% in drug-resistant individuals.

The distribution of the common biochemical and electrophysiological tests by epilepsy group is illustrated in Table 2. Except for newly diagnosed epilepsy, there was an increase in the number of assays with disease severity. For each epilepsy category, the most common biochemical test was plasma drug concentration, followed by blood cell count, transaminases, and creatinine levels. During the study period, there were 505 EEG recordings (newly diagnosed epilepsy, 200; epilepsy in remission, 115; active non–drug-resistant epilepsy, 42; drug-resistant epilepsy, 148). The proportion of special recordings (sleep, telemetry, video-EEG) tended to be higher in newly diagnosed patients (40%) compared with the other epilepsy categories (25, 31, and 28%). The use of EEG was correlated to the severity of the disease (Table 2). A total of 43 neuroradiologic examinations was performed during the study period in the entire sample (newly diagnosed epilepsy, 27; epilepsy in remission, five; active non–drug-resistant epilepsy, five; drug-resistant epilepsy, six).

The child neurologist was the leading consulting phy-

TABLE 1. *General characteristics of the sample by prognostic group*

	Total (189)		Newly diagnosed (63)	In remission (63)	Active non–drug resistant (21)	Drug resistant (42)
	No.	%	%	%	%	%
Sex						
M	96	50.8	47.6	50.8	47.6	57.1
F	93	49.2	52.4	49.2	52.4	42.9
Age (yr)[a]						
<5	38	20.1	38.1	9.5	9.5	14.3
5–14	119	63.0	55.6	66.7	71.4	64.3
>14	32	16.9	6.3	23.8	19.0	21.4
Disability[b]	41	21.7	3.2	15.9	9.5	64.3
Disability pension[b]	36	19.0	1.6	14.3	9.5	57.1
Assistant teacher[b]	45	23.8	1.6	20.6	28.6	59.5
Physical therapy[b]	44	23.3	6.3	20.6	19.0	54.8
Epilepsy syndrome[c]						
Partial	92	49.2	41.3	52.4	66.7	46.3
Generalized	85	45.0	49.2	44.4	33.3	45.2
Undetermined	7	3.7	4.8	1.6	—	7.1
Special	4	2.1	4.8	1.6	—	—
Etiology[b]	47	24.9	11.1	17.5	28.4	54.8
Associated illnesses[d]	31	16.4	7.9	15.9	19.0	28.6
Treatment at entry[b]						
None	24	12.7	31.7	6.3	—	—
Monotherapy	108	57.1	58.7	71.4	85.7	19.0
Polytherapy	57	30.2	9.5	22.2	14.3	81.0

Number of patients in parentheses.
[d] $p < 0.005$; [a] $p < 0.001$; [b] $p < 0.0001$ (Pearson's or Mantel–Haenszel's χ^2 test); [c] unknown in one case.

TABLE 2. *Laboratory and instrumental tests, medical consultations, and hospital admissions by prognostic group*

	Newly diagnosed (63) No./patient	In remission (63) No./patient	Active non–drug resistant (21) No./patient	Drug resistant (42) No./patient
Blood cell count[a]	2.3	1.4	2.3	4.0
Transaminases[a]	1.9	1.1	1.4	3.9
Creatinine[b]	1.7	0.9	1.0	2.7
Plasma drug concentrations	2.0	1.3	1.6	2.6
EEG[ac]	3.2	1.8	2.0	3.5
Medical consultations[d]	5.3	4.6	4.4	7.9
No. hospital admissions[e]	0.7	0.1	0.3	0.8
Days in hospital[f]	4.9	1.1	2.5	6.6
No. day-hospital admissions[b]	1.0	0.6	0.6	2.0

Number of patients in parentheses.
[c] Includes wake, sleep, telemetry and video EEG; [d] $p < 0.05$; [f] $p < 0.01$; [b] $p < 0.001$; [e] $p < 0.0005$; [a] $p < 0.0001$ (one-way analysis of variance).

sician, followed by the pediatrician. Epileptologic consultations accounted for 61% of the total visits; the corresponding values for epilepsy in remission, active non–drug-resistant, and drug-resistant epilepsy were 49%, 70%, and 48%, respectively. Drug-resistant patients had the highest consultation rates for the child neurologist, pediatrician, psychologist, physical therapist, and orthopedic surgeon.

Hospital admission and day-hospital were commonest in drug-resistant patients, who also had the highest number of days in hospital (6.6), followed by newly diagnosed patients (4.9). Valproate (VPA) was the commonest drug in each epilepsy category, followed by carbamazepine (CBZ; Table 3). Except for VPA (used in similar percentages across groups), each drug (including new compounds) was most common in drug-resistant patients. Felbamate (FBM) was given only in drug-resistant epilepsies. Six patients with newly diagnosed epilepsy had West syndrome. They were all treated with vigabatrin (VGB), and three of them also received adrenocorticotropic hormone (ACTH).

The annual cost of epilepsy management per person, based on the cumulative estimate of the expenses in the entire sample, was 1,767 Euros. Drug-resistant patients were the most expensive epilepsy category (3,268 Euros), followed by newly diagnosed patients (1,907 Euros), patients with active non–drug-resistant epilepsy (1,112 Euros), and patients in remission (844 Euros) (Table 4). The cost was similar in patients with drug-resistant epilepsy with and without associated disability (3,046 vs. 3,819 Euros). The same trend was evident in the three institutions. Except for active non–drug-resistant epilepsy, the cost for each category was higher in teaching-CR hospitals and lowest in outpatient services.

The cost ratio between teaching-CR hospital departments and outpatient services was 4.0 for newly diagnosed patients, 3.4 for patients with occasional seizures,

TABLE 3. *Drug consumption by prognostic group*

	Newly diagnosed (63)		In remission (63)		Active non–drug resistant (21)		Drug resistant (42)	
	No. cases[a]	%	No. cases[a]	%	No. cases[a]	%	No. cases[a]	%
Barbiturates	5	8	8	13	2	10	9	21
Carbamazepine	14	22	16	25	8	38	15	36
Phenytoin	—	—	—	—	—	—	2	5
Valproate	39	62	37	59	13	62	25	60
Gabapentin[b]	1	2	—	—	1	5	10	24
Lamotrigine[c]	4	6	4	6	1	5	13	31
Vigabatrin[d]	11	17	9	14	1	5	13	31
Ethosuximide	6	10	3	5	1	5	6	14
Felbamate[b]	—	—	—	—	—	—	9	21
Benzodiazepines[b]	6	9	3	5	2	9	18	43
ACTH	4	6	1	2	—	—	3	7

Number of patients in parentheses.
[a] Number of cases treated with specific drug.
[d] $p < 0.05$; [c] $p < 0.0005$; [b] $p < 0.0001$ (Pearson's χ^2 test).

TABLE 4. *Annual cost (in Euro) per patients by prognostic group*

	Newly diagnosed (63)			In remission (63)			Active non–drug-resistant (21)			Drug resistant (42)		
	Cost/patient	(SEM)	%	Cost/patient	(SEM)	%	Cost/patient	(SEM)	%	Cost/patient	(SEM)	%
Hematochemical assays[a]	41	(7.0)	2	25.8	(4.1)	3	34.4	(6.7)	3	58.7	(10.7)	2
Instrumental exams	81.4	(13.7)	4	64.6	(17.0)	8	41.3	(13.8)	4	45.5	(10.4)	1
Medical consultations	70.3	(7.8)	4	74.3	(18.6)	9	56.2	(10.3)	5	87.2	(17.1)	3
Hospital admissions[b]	1,234.7	(219.5)	65	219.5	(82.9)	26	576.2	(217.8)	52	1,358.2	(303.5)	41
Day-hospital admissions[c]	294.1	(82.9)	15	168.7	(42.2)	20	188.0	(92.5)	17	621.9	(139.2)	19
Drugs[d]	185.7	(27.4)	10	290.9	(46.4)	34	216.1	(50.9)	19	1,096.10	(166.1)	34
New drugs[d]	96.8	(27.4)	5	162.7	(47.6)	19	79.8	(48.7)	7	927.7	(169.1)	28
Total[d]	1,907.1	(27.4)	100	843.8	(109.6)	100	1,112.3	(254.0)	100	3,267.6	(367.8)	100
University hospitals	2,660.9	(445.2)		1,229.1	(279.3)		1,750.1	(495.5)		3,616.6	(433.5)	
General hospitals	2,190.4	(638.3)		799.8	(126.9)		1,767.6	(875.4)		2,931.8	(696.9)	
Outpatient services	662.9[e]	(158.8)		500.7	(176.9)		526.1	(153.7)		2,611.0	(1,165.7)	

Number of patients in parentheses. New drugs include felbamate, gabapentin, lamotrigine, and vigabatrin.
SEM, Standard error of the mean, %, percentage of total cost of prognostic group.
[a] $p < 0.05$; [b] $p < 0.0005$; [c] $p < 0.001$; [d] $p < 0.0001$; (one-way analysis of variance).
[e] $p < 0.01$ (one-way analysis of variance comparing the three institutions within each prognostic group).

2.5 for patients in remission, and 1.4 for drug-resistant patients. The costs for general hospitals tended to be closer to those of teaching departments for newly diagnosed patients and intermediate for patients in remission and with drug-resistant epilepsy.

No significant differences were present across institutions regarding the distribution of the individual resources consumed (data not shown). Hospital admissions and day-hospitals were the major cost in all epilepsy groups, and peaked in newly diagnosed patients (80% of the entire cost; Table 4). Drugs ranked second, ranging from 10% (newly diagnosed patients) to 34% (drug-resistant patients and patients in remission). The percentage of the cost of treatment attributable to new AEDs tended to vary across groups (newly diagnosed, 52%; remission, 56%; active non–drug-resistant, 37%; drug-resistant, 85%). Laboratory and instrumental tests and medical consultations represented a small proportion of total costs across all epilepsy groups.

DISCUSSION

Our study cannot be easily compared with the published reports because of the differences in the target population, study design, and national or local socioeconomic setting. Methodologic issues are the most common explanation for the different cost estimates across published reports (2,6).

Even with these limitations, our estimates of the annual cost of epilepsy management per person (1,767 Euros) are fairly comparable to those of the Italian Episcreen Project, a multicenter longitudinal study involving 15 referral epilepsy centers (7). In that study, the average direct annual cost per child was 2,227 U.S. dollars. The difference can be explained mostly by the different study population (patients in remission, who were 33% of our sample, might have been less frequent in the Episcreen centers). This study is in keeping with a U.S. disease model of the costs of epilepsy (8), which showed that the direct cost for the first year of disease is 2,468 U.S. dollars. In our study, the cost of newly diagnosed epilepsy was 2,190 Euros for patients seen in general hospitals and 2,661 Euros in those seen in teaching-CR hospitals. Our data from the university and the general hospitals are also close to those of the French prospective cohort study of patients with newly diagnosed epileptic seizures (9). In that study, in which the participants were neurologists and child neurologists throughout France, the mean epilepsy-related direct costs for the first year of disease in patients younger than 16 years were 1,564 F (= 2,346 Euros). This sample also revealed the mean annual cost of drug-resistant epilepsy was 3,268 Euro, which was roughly comparable to the cost of those with refractory partial epilepsy given VGB in Sweden (10). In that sample, the cost of VGB was 53% of the total annual health care cost (treatment cost accounted for 34% in our sample). By contrast, the annual cost of refractory epilepsy in a U.S. incident cohort was 4,116 U.S. dollars (treatment cost, 11%) (11).

Our study also tends to confirm in children the results of reports conducted mostly in adults with epilepsy, which showed that seizure frequency and response to treatment are significantly correlated with the health care costs of epilepsy (8,12–14).

In line with the U.K. investigations (12,14), the greatest source of direct costs was that of hospital-based care, followed by drug treatment. The different use of hospital facilities across institutions (teaching-CR hospitals preferring day-hospital for many outpatient activities) may explain the cost differences in the absence of a differential distribution of the resources.

In our study, new AEDs accounted for 37–85% of the entire cost of treatment, with a peak among drug-resistant patients. In the study of Jacoby et al. (1998) (14), the percentage of cost attributable to new AEDs ranged from 15% (patients in remission) to 59% (patients with more than one seizure per month). Also the use of VGB and lamotrigine (LTG) accounted for 46% of the

entire treatment cost in patients with epilepsy attending a specialist epilepsy service (15). Cost-effectiveness and cost-minimization studies report that new AEDs may be associated with an overall reduction in the use of medical care resources (16,17). However, even a more rational use of old AEDs has been reported to be followed by cost savings (18–20). In addition, no evidence is yet available showing that the higher cost of new AEDs translates into cost savings in the short- and long-term periods. However, the use of new AEDs may be necessary for patients for whom old drugs are failing. The issue can be settled only by comparing old and new drugs for patients with disease of comparable severity. The direct costs of epilepsy tended to be significantly different when comparing teaching-CR hospitals with general hospitals and outpatients services. Although a significant cost difference may be accepted for drug-resistant patients, this is not true for the other prognostic groups. Our findings are in line with the results of a recent study on the cost of epilepsy in the United States (21). In that study, a cost-of-illness analysis was performed relying on information provided by a panel of experienced epilepsy clinicians. Based on the estimated resource utilization, the annual cost of epilepsy was lower in patients treated by generalists compared with specialists, regardless of the setting (Medicare vs. private) and the year of observation (first vs. subsequent).

It has been suggested that the health care system should provide mechanisms facilitating consultations among primary-, secondary-, and tertiary-level health care providers (22). On this basis, we might suggest that people with uncomplicated epilepsy be referred to outpatient services, and only those who present complicated and/or drug-resistant epilepsy be attended by general hospital or university hospital staff. Sometimes, despite its higher cost, the day-hospital may be a convenient strategy for the management of selected problems in patients with epilepsy. In these cases the cost-effectiveness ratio of a given medical intervention is not correlated to its practical implications.

In our sample, 16% of cases had associated clinical conditions. Disability (with pension), or special support at school, and rehabilitative measures could be related at least in part to these conditions. Many reports on the costs of epilepsy do not take into account the effects of other illnesses. This bias is potentially large, as the prevalence of multiple conditions is high among referral patients with epilepsy (23). However, attribution of direct costs to epilepsy could be determined only with proper investigation of the cause for each medical encounter or by matching epilepsy cases to a control population without epilepsy (24).

Further investigations using the same design in different study populations are thus awaited to calculate the direct costs attributable to epilepsy in pediatric and adult patients and the comparison of different socioeconomic settings.

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