Am. J. Hum. Genet. 74:121–127, 2004

The Burden of Genetic Disease on Inpatient Care in a Children's Hospital

Shawn E. McCandless,[1,2] Jeanne W. Brunger,[3] and Suzanne B. Cassidy[4]

[1]Department of Genetics, Case Western Reserve University, Cleveland; [2]Center for Human Genetics and Department of Pediatrics, University Hospitals of Cleveland, Cleveland; [3]Clinical Genetics Service, Department of Cancer Genetics, Roswell Park Cancer Institute, Buffalo, NY; and [4]Department of Pediatrics, Division of Human Genetics, University of California, Irvine, School of Medicine, Irvine, CA

The important role of genetics in pediatric illness has been increasingly recognized, but the true impact has not been well delineated. An important study of pediatric inpatient admissions to a children's hospital in 1978 found a genetic basis for disease in just less than half of admitted patients. We sought to update this study in light of current hospitalization practices and new knowledge about genetics. We systematically reviewed the records of 5,747 consecutive admissions (4,224 individuals), representing 98% of patients admitted in 1996 to Rainbow Babies and Children's Hospital (Cleveland, OH). Each patient was assigned to one of five groups on the basis of the presence or absence of an underlying chronic medical condition and whether that condition had a genetic basis or susceptibility. An underlying disorder with a significant genetic component was found in 71% of admitted children. The vast majority (96%) of underlying chronic disorders in children in this study were either clearly genetic or had a genetic susceptibility. Total charges for 1996 were >$62 million, of which $50 million (81%) was accounted for by disorders with a genetic determinant. The 34% of admissions with clearly genetic underlying disorders accounted for 50% (>$31 million) of the total hospital charges. The mean length of stay was 40% longer for individuals with an underlying disease with a genetic basis than for those with no underlying disease. Charges and length of stay were similar for children with underlying chronic disorders, regardless of the cause. This study begins to quantify the enormous impact of genetic disease on inpatient pediatrics and the health care system. Additional study and frank public discourse are needed to understand the implications on the future health care workforce and on the utilization of health care resources.

Introduction

Individual genetic disorders are rare, but, in the aggregate, genetic disorders are common. One of the recurring themes of the era of the Human Genome Project is the growing recognition of the complexity of the genetic and molecular basis of disease. Accumulating evidence even suggests that susceptibility to infections and disorders like hemolytic uremic syndrome may be genetically determined (Rougier et al. 1998; Noris et al. 1999). An annual review of pediatric mortality data shows that 23% of infant deaths are due to genetically determined disorders (Hoyert et al. 2001). In a study from Scotland published in 1991, as many as 70% of children who were admitted to a pediatric intensive care unit had partly or wholly genetically determined disorders (FitzPatrick et al. 1991). In the past 30 years, a variety of investigators, utilizing different approaches, have examined the burden of genetic disease and congenital anomalies in samples of inpatients of all ages (Day and Holmes 1973), in neonatal intensive care settings (Ling et al. 1991; Ling 1992), in pediatric intensive care settings (FitzPatrick et al. 1991; Cunniff et al. 1995), among pediatric inpatients (Scriver et al. 1973; Hall et al. 1978; Carnevale et al. 1985; Yoon et al. 1997), and in a large cohort of consecutively born children (Chung and Myrianthopoulos 1987). More than 25 years ago, Hall et al. (1978) performed a landmark study of 4,100 admissions to a pediatric hospital, finding that just over half were for a genetically determined condition, with 4.5% being due to wholly genetic disorders, 22% due to multifactorial or polygenic disorders, and 27% due to developmental or familial disorders. Patients with genetically determined disorders stayed in the hospital longer and had more expensive admissions.

Changes in health care delivery in the past 25 years, especially trends toward outpatient care of uncomplicated problems and a greater understanding of the genetic basis of many disorders, may lead to a higher proportion of genetic disease among pediatric inpatients. We recently conducted a study of the burden of genetic disease similar to that of Hall et al. in a pediatric inpatient population. Specifically, we set out to determine the proportion of pediatric admissions with an underlying chronic condition and what proportion of those have a genetic determinant.

Received August 6, 2003; accepted for publication October 27, 2003; electronically published December 12, 2003.

Address for correspondence and reprints: Dr. Shawn E. McCandless, Center for Human Genetics, University Hospitals of Cleveland/Case Western Reserve University, 11100 Euclid Avenue, 1500 Lakeside, Cleveland, OH 44106. E-mail: shawn.mccandless@cwru.edu

0002-9297/2004/7401-0012$15.00

Subjects and Methods

The study was performed at Rainbow Babies and Children's Hospital (Cleveland, OH), a full-service children's hospital with 244 pediatric inpatient beds. The hospital is part of University Hospitals of Cleveland, and its patient population includes primary care for many parts of Cleveland, as well as tertiary care for northeastern OH. The protocol was reviewed and approved by the institutional review board. We reviewed the records of every child ≤18 years of age admitted in calendar year 1996, the latest year for which complete discharge records were available and computerized at the time the study began. A computerized database capturing a variety of demographic, medical, and financial data for each admission was maintained by the health information service at University Hospitals of Cleveland. These records formed the initial database for this study.

Figure 1 shows a flowchart of the study's design. Pregnancy-related diagnoses, including deliveries, newborn care, and neonatal intensive care, were excluded because the purpose of the study was to evaluate children admitted to a pediatric inpatient unit. All other children ≤18 years of age were included. Each patient's record was reviewed until a genetic diagnosis was identified or eliminated. Each admission was assigned to a category on the basis of the presence or absence of an underlying disorder, whether or not it was the proximate cause of the admission, and the extent to which that disorder was genetically determined.

Table 1 shows the categories used, definitions, and examples of each category. A complete list of the assigned diagnoses in each category is available as an online supplement (appendix A). These categories were modified from those defined by Hall et al. (1978), to allow for increased recognition of the genetic contribution to various chronic medical conditions. Category I includes individuals with a congenital underlying condition, with various subcategories designed to further refine the genetic component. Category II includes individuals with birth defects that are not known to have a genetic basis, including teratogenic effects. It should be noted that this classification does not imply that possible genetic causes have been disproved, only that current evidence is not strong for an underlying genetic cause. Category III includes individuals with those acquired disorders for which the medical literature and clinical experience suggest a genetic component, predisposition, or genetically determined susceptibility. Category IV includes individuals with an acquired chronic underlying condition with no recognized genetic component. Category V includes those children with no preexisting chronic medical condition of any kind (genetic or nongenetic)—that is, previously healthy children admitted for an acute illness or injury.

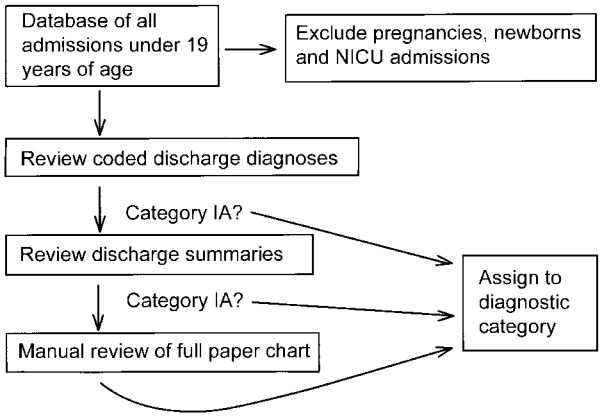

Figure 1 Flowchart of the record-evaluation process

The initial review, using only the discharge diagnoses listed in the computerized database, identified those inpatients with an underlying disorder that was clearly genetically determined, such as trisomy 21 or cystic fibrosis. These diagnoses were assigned to category I-A (see table 1). The second level of review looked at computerized discharge summaries for those admissions that could not be assigned to category I-A on the basis of discharge diagnoses alone; additional documentation

Table 1

Definitions of Categories

Category	Definition	Examples
I	Underlying conditions with strong genetic basis	
I-A	Single-gene or chromosomal	Cystic fibrosis, sickle cell disease, chromosome anomaly
I-B	Multifactorial/polygenic	Congenital heart disease, cleft lip/palate, Hirschsprung disease
I-C	Heterogeneous causes, often genetic	Mental retardation, seizures
II	Birth defects without known genetic basis	
II-A	Malformations of unknown etiology	Bladder exstrophy
II-B	Teratogenic disorders	Congenital cytomegaloviral infection, fetal alcohol-related disorder
III	Acquired disorders with genetic predisposition	Asthma, diabetes, cancer
IV	Acquired disorders without genetic determinant	Hypoxic-ischemic brain injury
V	No preexisting chronic medical condition	Acute trauma or infection in previously healthy child

Table 2

Comparison of Data from Charts That Were Not Available with Data from All Available Charts

	Average Value (95% CI)		
Chart	Daily Charge	Length of Stay [d]	Age [d]
Not available (n = 112)	$14,939 ($5,507–$24,370)	5.33 (2.61–8.05)	1,705 (1,368–2,042)
All others (n = 5,635)	$10,837 ($10,008–$11,665)	4.77 (4.49–5.05)	2,523 (2,465–2,581)

of a clearly genetic disorder was sought so that the chart could be assigned to the most appropriate category. For all records that could not be assigned to category I-A from the discharge diagnoses or the discharge summary, the entire written medical chart was manually reviewed, abstracted, and systematically evaluated. This review of the written record included all previous admissions and available outpatient-clinic notes. Categories were assigned on the basis of the presence and etiology of any underlying chronic medical condition in the admitted patient. The charts were abstracted by one of three research associates. Assignment of a particular diagnosis to a category was made by one of the medical geneticists (S.B.C. or S.E.M.). The research associate assigned additional occurrences of the same diagnosis to the previously determined category without review by the medical geneticists. In many cases, a diagnosis could not easily be assigned to a category. The research associate and the two geneticists conferred on those cases in detail, and assignment was made using available resources, such as Mendelian Inheritance in Man, both the online (OMIM) and bound versions (McKusick 1998).

Yoon et al. (1997) generated a list of ICD-9 (International Classification of Diseases, Revision 9) codes for "birth defects and genetic disorders" for a study looking at computerized databases of all pediatric discharges for 1 year from hospitals in CA and SC (Yoon et al. 1997). (The codes are available as an online supplement [appendix B].) We searched our computerized data set of discharge ICD-9 codes, using the same list of codes. The results of this computerized search were compared to the results of the manual chart review described above.

Descriptive statistics were calculated for total charges, average daily charge, and length of stay. The 95% CI was calculated for each value. Comparisons of mean values were considered statistically significant when there was no overlap in the calculated 95% CIs. Microsoft Excel was used for all statistical analyses.

Results

There were 9,904 admissions in 1996, of which 4,045 were excluded because they involved perinatal care, either a teen admitted for pregnancy-related care or a neonate. An additional 112 admissions (<2%) were excluded because charts were unavailable. This group was not significantly different from the whole in terms of charges or length of stay, as shown in table 2, although the average age of the patients was significantly less in those for whom charts were not available.

A total of 5,747 admissions were reviewed, representing 4,224 individuals, some of whom were admitted more than once. Data were recorded for each admission for those individuals. The full record was reviewed for >5,000 admissions. Data are summarized in table 3.

Figure 2 shows the number of admissions in each category. There were 1,949 admissions in category I. This represents ~34% of the total admissions. The largest single group, with 37% of the total admissions, was category III, disorders with a genetically determined predisposition or susceptibility. There were few admissions in categories II and IV, birth defects and acquired disorders, respectively, with no known genetic component (2.5% combined). Finally, ~27% of admissions were previously healthy children (category V).

Diagnoses in Category I-A

Figure 3 shows the types of disorders in category I-A (chromosomal and single-gene disorders). Of the 74 admissions of patients with chromosomal disorders, 51 (69%) had trisomy 21, 7 (9.4%) had trisomy 13, 3 (4%) had trisomy 18, 2 (2.7%) had sex-chromosome abnormalities, and 11 (14.9%) had other chromosome rearrangements. The 44% of admissions in the "Other" category had one of >75 different single-gene disorders (details available as an online supplement [appendix A]).

Length of Stay

Figure 4 shows the average length of stay for admissions in each category. Children with single-gene and chromosomal disorders (category I-A) had an average hospital stay (7.1 d) that was twice as long as the 3.5-d average stay for children without any preexisting chronic medical disorder (category V). All of the other genetic categories also had average lengths of stay that were longer than children in category V. These differences have nonoverlapping 95% CIs (see table 3).

Average Charge per Admission

Table 3 shows the combined charges for each of the categories and the subgroups of category I. The differ-

ences between each subgroup of category I and category V (no underlying condition) are highly statistically significant, as is the difference between category III (acquired disorders with genetic predisposition) and category V. The differences in average charges between category II subgroups and category V and between category IV and category V do not reach statistical significance. The numbers of admissions in both categories II and IV were small relative to the other categories, making comparisons less meaningful. The average cost for category IV was increased by 50% by the inclusion of a single patient with a prolonged stay of 176 d.

Charges by Category

Figure 5 shows the total charges for each category, and figure 6 represents the average charge per hospital day. For the year of the study, a total of $62.3 million in charges were generated, of which nearly $50 million (80%) were attributed to the genetic categories (I-A, I-B, I-C, and III), which accounted for 71% of the admissions. The wholly genetic categories (I-A, I-B, and I-C), which made up one-third of admissions, accounted for almost $31 million, or 50% of the total. Add to that those children with an underlying disorder with a genetic predisposition (category III), and hospital expenses for children with genetically determined illnesses accounted for nearly $50 million, or 80% of the total hospital charges for the year.

Diagnosis Identification Using ICD-9 Codes Only

Using the ICD-9 codes for genetic disorders defined by Yoon et al. (1997) to search our database identified 1,490 admissions as having a genetic basis. (The codes are available as an online supplement [appendix B].) The diagnoses listed in that series primarily fall in our category I. We identified 1,949 admissions in category I, so the strategy of using a computerized search of discharge ICD codes identified only 76.4% of the diagnoses identified by a full review of the charts for clearly genetic disorders. The computerized search of ICD-9 codes does not include category III, a category of diseases for which there is a strong genetically determined predisposition or susceptibility.

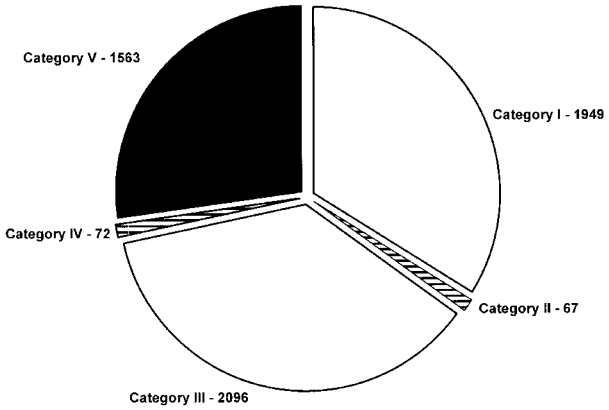

Figure 2 Admissions in each category. The same illustration schema is used in figures 2, 4, 5, and 6. Those categories with a strong genetic contribution (categories I and III) are shown in white. Those categories with no genetic component, or for which there is controversy (categories II and IV), are denoted by horizontal stripes. Admissions of previously healthy children with no preexisting chronic medical condition (category V) are shown in black.

Discussion

This study begins to quantify the enormous impact of the genetic determinants of disease on inpatient pediatrics and the health care system. We found that, in a full-service pediatric inpatient facility, more than two-thirds of admissions and 80% of the charges are attributable to diseases that have a recognized genetic component. Children with genetically determined conditions

Table 3

Summary of Data

Category	No. of Patients	Average Age [years] (95% CI)	Average Length of Stay [d] (95% CI)	Average Charge (95% CI)
I-A	622	7.7 (7.2–8.2)	7.1 (6.0–8.2)	$17,218 ($13,234–$21,440)
I-B	832	5.0 (4.6–5.4)	6.4 (3.8–7.8)	$17,290 ($5,647–$12,725)
I-C	495	6.1 (5.5–6.6)	4.9 (5.2–7.5)	$11,413 ($14,044–$20,355)
II-A	48	2.8 (1.5–4.0)	5.8 (3.8–7.8)	$9,186 ($2,274–$29,273)
II-B	19	5.8 (3.1 –8.5)	5.5 (1.5–9.5)	$15,774 ($9,553–$13,273)
III	2,096	8.0 (7.8–8.3)	4.3 (3.8–4.7)	$8,904 ($7,744–$10,063)
IV	72	6.8 (5.2–8.3)	7.6 (2.7–12.3)	$16,857 ($6,988–$26,725)
V	1,563	6.6 (6.3–6.9)	3.5 (3.3–3.7)	$6,985 ($6,306–$7,664)
I-A, I-B, I-C[a]	1,949	6.1 (5.9–6.4)	6.2 (5.6–6.8)	$15,774 ($13,735–$17,500)
II-A, II-B[b]	67	5.4 (4.4–6.4)	5.7 (3.9–7.6)	$11,054 ($5,022–$15,602)

[a] Represents the combination of the three subgroups of category I.
[b] Represents the combination of the two subgroups of category II.

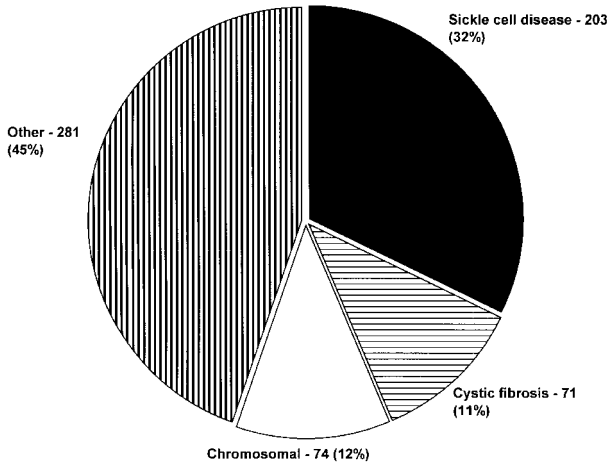

Figure 3 Diagnoses included in category I-A

also stay in the hospital longer than do children without a preexisting chronic medical condition.

The strengths of this study are the large number of admissions and the fact that >98% of the admissions for a full year were reviewed for indication of an underlying genetic component, even when it was not included in the discharge diagnoses. This gives excellent statistical strength to the findings and adds to the accuracy of the results. For example, using the ICD-9 code for "chromosome anomaly—not otherwise specified (NOS)" in a computerized search would potentially classify as category I-A patients with tumors that contain chromosomal rearrangements. Likewise, to obtain complete data capture, this method relies on the inclusion of all possible diagnoses in the discharge face sheet. It was clear from our review that this was not the case. The incidence of the discharge diagnoses inaccurately reflecting all underlying conditions was not recorded during the data-collection phase of the study, so we cannot state with certainty the frequency of diagnoses missed by the hospital coders in our data set. A recent study of a database of discharge ICD-9 codes from all pediatric admissions in CA and SC (Yoon et al. 1997) found significantly lower numbers than those found by Hall et al. (1978) or the current study. That study was complicated by the fact that the researchers relied on computerized records of billing codes, and they did not take into account complex genetic traits and inherited predisposition/susceptibility to disease. We searched our data set, using the list of ICD-9 codes generated for that study. This analysis identified 1,490 admissions in our data set as having a genetically determined disorder coded in the discharge diagnoses. Since the diagnoses used primarily fit into our category I, this strategy underestimated the true frequency in our population of even that limited group of genetic disorders by almost 25%. One could also argue that physicians and coders in a tertiary-care children's hospital are more likely to accurately capture and code genetic diagnoses than are providers in a community hospital. This suggests that the strategy used by Yoon et al. (1997) may lead to even more underascertainment in that data set than in ours. Also, that strategy does not include the large group of disorders that are partially genetically determined, classified in our category III. Our analysis, therefore, provides a more complete evaluation of the genetic contribution to disease in the population studied. The difficulty of applying our approach to a statewide data set is obvious, and it is clear that both approaches can inform the discussion of the contribution of genetics to pediatric disease.

There are several drawbacks to the current study. First, only inpatients in a single children's hospital were analyzed; second, the evaluation was done retrospectively; and third, the categorization was based solely on what the providers wrote in the charts. In spite of these drawbacks, the findings are consistent with those of Hall et al. (1978) from 25 years ago in an entirely different geographical area.

These data do not include pregnancy-related admissions in teenagers, neonates, or patients admitted to the neonatal intensive care unit, either inborn or outborn, even though these data were available. Neonates were excluded from the study for several reasons. First, the purpose of the study was to determine the burden of

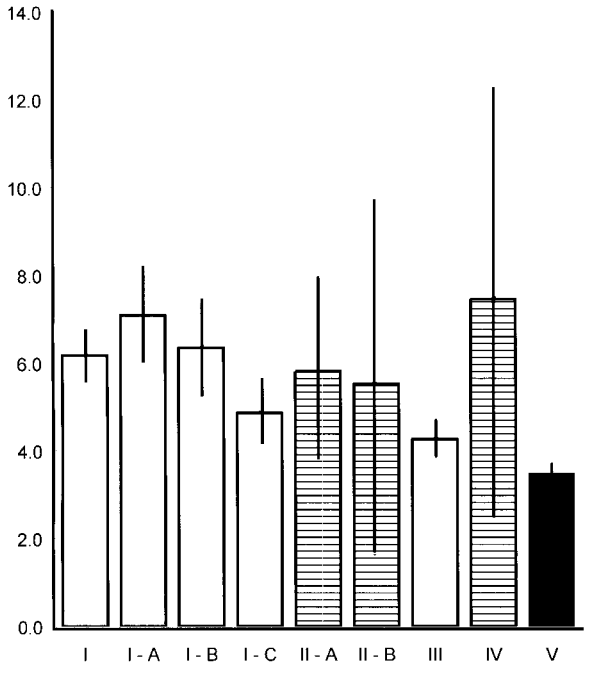

Figure 4 Length of stay (in days). Mean values are shown by a bar; the vertical lines represent the 95% CIs.

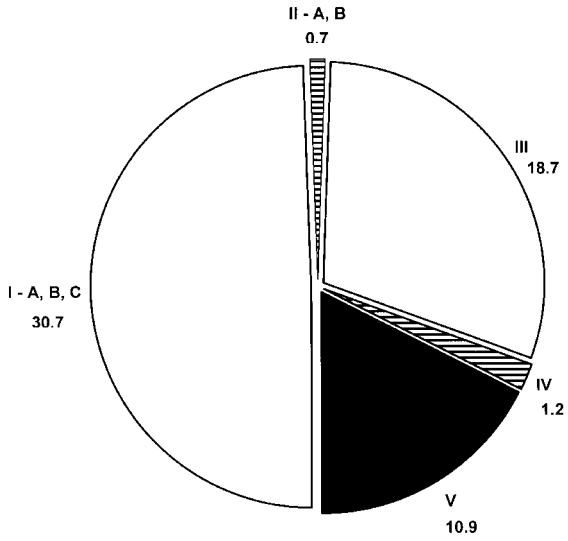

Figure 5 Total charges by category. The values shown represent millions of dollars.

genetic disease among patients *admitted* to the hospital for the care of illness. Thus, there was an obvious and real difference between the populations of pregnant mothers and newborns admitted to the nursery and the population admitted to the inpatient unit. The bias introduced by including these patients would make the results uninterpretable. Infants admitted to the neonatal intensive care unit presented the opposite dilemma. There were few, if any, admissions of "previously healthy" infants to the neonatal intensive care unit. This raised concern about the validity of the conclusions drawn from the data—specifically, that children with underlying conditions would be overrepresented in the data. Also, as the initial review began, it became clear that the practical difficulties of assigning the neonates to the categories would make the current study unfeasible. The neonatal intensive care unit population merits its own study, with criteria designed specifically for that population, as has been initially addressed by Ling et al. (1991).

In total, 71% of patients admitted to this children's hospital had an underlying disorder that is known to be at least partly genetically determined. Equally striking is the fact that, of patients with a preexisting underlying condition, >96% had a disorder that was, at least in part, genetically determined (categories I-A, I-B, I-C, and III). Genetically determined diseases were almost evenly divided between those that have clear-cut genetic determinants (48.2% with single-gene, chromosomal, polygenic, or multifactorial disorders) and those for which there is a well-recognized genetically determined predisposition (51.8%).

This information raises important issues regarding the genetic contribution to chronic health disorders, in general. We focused on a population of convenience—namely, pediatric inpatients. It seems likely that the findings would be similar if one were to look at chronic diseases in a purely primary-care outpatient pediatric population and perhaps even in an adult population. Strategies to perform studies such as these need to be carefully conceived to avoid the pitfalls of large, computerized database searches of billing codes. That type of study is highly dependent on coding practices and is likely to miss many genetic disorders, particularly those of multifactorial or polygenic inheritance, complex genetic traits, or disorders with epidemiologically described genetic predisposition.

This study confirms and updates what Hall et al. (1978) found >25 years ago—that genetic disorders are common, and that the cost to individuals and society is high. Not surprisingly, the majority of children admitted to a children's hospital have an underlying chronic illness, and these children have longer hospital stays and higher hospital expenses than children without underlying disorders. One of the most striking findings of this study is that 96% of those chronic disorders

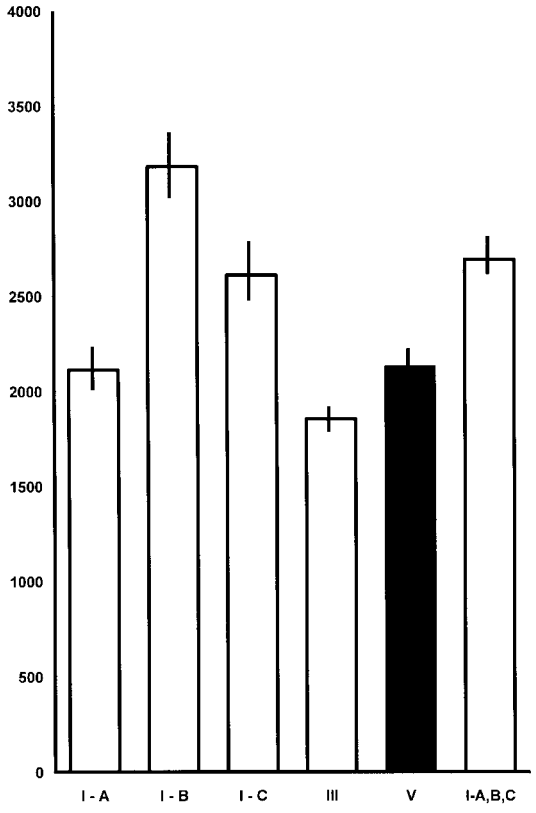

Figure 6 Average charge (in dollars) per hospital day. Mean values are shown by a bar; the vertical lines represent the 95% CIs.

of childhood are partly or wholly genetically determined. We feel that this fact is not widely recognized and that the impact is not fully appreciated by health care providers, payers, and policy makers (Hall 1997).

Conclusions

In a children's hospital, genetic diseases are common, not rare. The public appears to have a strong interest in understanding the impact of new knowledge of genetics and molecular biology on their lives and their illnesses. The current workforce of specialty-trained genetics providers seems insufficient to meet the expected increasing need. In addition to a larger genetic workforce, every person providing care to children, and to adults, will need to be

- fluent in the language of molecular biology and genetics,
- able to grasp the complexities of genetic information when applied to health and disease,
- competent to explain these complexities to an anxious public and to discuss their implications with affected families,
- knowledgeable about the power and potential pitfalls of genetic testing and the implications of the results for the individual and the family,
- informed about the promises and actualities of therapies for genetic disorders, including gene transfer and progenitor cell transfer approaches, and
- cognizant of the complex legal, ethical, and privacy issues raised by the characterization of an individual's genetic makeup.

This will require significant changes in the processes of medical education at all levels of training and a real commitment from health care providers to make the effort to become conversant in genetic concepts. In the not-so-distant future, medical practitioners will need to be as comfortable discussing SNPs and proteomics as they now are discussing germs and antibiotics.

Acknowledgments

The Rainbow Corporation provided funding for this study. The authors thank the Health Records Department at University Hospitals of Cleveland for a tremendous effort in tracking down and delivering >4,000 paper charts, some more than once, many of multiple volumes. Deborah Dawson, Ph.D., assisted in understanding the database and advising on its utilization for the study. We also thank Arthur S. Aylsworth, M.D., and H. Neil Kirkman, M.D., for their helpful comments. Samarah Moussavand and Christin Dietz performed a portion of the record reviews.

Electronic-Database Information

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

References

Carnevale A, Hernandez M, Reyes R, Paz F, Sosa C (1985) The frequency and economic burden of genetic disease in a pediatric hospital in Mexico City. Am J Med Genet 20:665–675

Chung CS, Myrianthopoulos NC (1987) Congenital anomalies: mortality and morbidity, burden and classification. Am J Med Genet 27:505–523

Cunniff C, Carmack JL, Kirby RS, Fiser DH (1995) Contribution of heritable disorders to mortality in the pediatric intensive care unit. Pediatrics 95:678–681

Day N, Holmes LB (1973) The incidence of genetic disease in a university hospital population. Am J Hum Genet 25:237–246

FitzPatrick DR, Skeoch CH, Tolmie JL (1991) Genetic aspects of admissions to a paediatric intensive care unit. Arch Dis Child 66:639–641

Hall JG (1997) The impact of birth defects and genetic diseases. Arch Pediatr Adolesc Med 151:1082–1083

Hall JG, Powers EK, Mcllvaine RT, Ean VH (1978) The frequency and financial burden of genetic disease in a pediatric hospital. Am J Med Genet 1:417–436

Hoyert DL, Freedman MA, Strobino DM, Guyer B (2001) Annual summary of vital statistics: 2000. Pediatrics 108:1241–1255

Ling EW (1992) Frequency and load of congenital anomalies in a neonatal intensive care unit, prenatal diagnosis, and perinatal management. Semin Perinatol 16:352–357

Ling EW, Sosuan LC, Hall JC (1991) Congenital anomalies: an increasingly important cause of mortality and workload in a neonatal intensive care unit. Am J Perinatol 8:164–169

McKusick V (ed) (1998) Mendelian inheritance in man: a catalog of human genes and genetic disorders. 12th ed. Johns Hopkins University Press, Baltimore

Noris M, Ruggenenti P, Perna A, Orisio S, Caprioli J, Skerka C, Vasile B, Zipfel PF, Remuzzi G (1999) Hypocomplementemia discloses genetic predisposition to hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: role of factor H abnormalities. Italian Registry of Familial and Recurrent Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura. J Am Soc Nephrol 10:281–293

Rougier N, Kazatchkine MD, Rougier JP, Fremeaux-Bacchi V, Blouin J, Deschenes G, Soto B, Baudouin V, Pautard B, Proesmans W, Weiss E, Weiss L (1998) Human complement factor H deficiency associated with hemolytic uremic syndrome. J Am Soc Nephrol 9:2318–2326

Scriver CR, Neal JL, Saginur R, Clow A (1973) The frequency of genetic disease and congenital malformation among patients in a pediatric hospital. Can Med Assoc J 108:1111–1115

Yoon PW, Olney RS, Khoury MJ, Sappenfield WM, Chavez GF, Taylor D (1997) Contribution of birth defects and genetic diseases to pediatric hospitalizations. A population-based study. Arch Pediatr Adolesc Med 151:1096–1103