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American Journal of Family Medicine

RECEIVED: DECEMBER 10, 2017
ACCEPTED: JANUARY 10, 2018
PUBLISHED: JANUARY 20, 2018

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KEYWORDS

Family practice; Symptom assessment; Complexity; Diagnostic techniques and procedures; Longitudinal data; Longitudinal study; Qualitative; Case study method

CITATION

Jose Luis Turabian 2018. Longitudinal Study of a Series of Cases on Trajectory of the Chain of Accumulating Health Problems in Certain People. Am J Family Med. 2018. 1(1) 1001

RESEARCH ARTICLE

LONGITUDINAL STUDY OF A SERIES OF CASES ON TRAJECTORY OF THE CHAIN OF ACCUMULATING HEALTH PROBLEMS IN CERTAIN PEOPLE

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Abstract

Objective

The general objective was to obtain new evidences and generate theory by contrasting existing hypotheses about the accumulation of diseases in certain patients.

Participants and methods

A qualitative and quantitative, longitudinal, descriptive, and retrospective case series study based on a single cohort was carried out, in a family medicine office in Toledo, Spain. A convenience sample was selected with a careful choice of cases with "multimorbidity", until the saturation of the data. An analysis of the content of medical record, other documents such as the specialist reports and physician-patient interview data was carried out, to assign each health problem to a certain hypothesis of accumulation of diseases according the following classification:

1. Causality, associations and linkages

2. Coincidences, seriality, or synchronicity

3. Concurrent (random or chance); and

4. Iatrogenesis and complication. Gantt charts were drawn to visualize the pattern of disease accumulation over time in each patient.

Results

There were 18 cases, 9 men (age range: 39-89 years), and 9 women (age range: 31-76 years). The accumulation of health problems occurs in the 63% of the time by Causality, associations and linkages, in 22 % by random or chance, in 11% by Iatrogenesis and complication, and in 4% by Coincidences, seriality or synchronicity. In the trajectory of accumulation of diseases, Causality, associations and linkages predominate in all phases; Concurrent hypotheses (random or chance) predominate in the initial phases, and Iatrogenesis and Complication predominate in the final phases.

Conclusions

1) the mechanism due to causality, associations and linkages supposes more than half of the reasons of accumulation of diseases, but the mechanism by iatrogenesis and complication supposes more than 10% of causes of accumulation of diseases; 2) both mechanisms are susceptible to being prevented; and 3) the accumulation of diseases or multimorbidity in certain people may be in part a phenomenon self-created by the health intervention itself.

"You will not apply my precept," he said, shaking his head. "How often have I said to you that when you have eliminated the impossible whatever remains, however improbable, must be the truth?

Arthur Conan Doyle. The Sign of the Four.

Introduction

Although there are methodological problems to assess the prevalence of multimorbidity [1-8], the triangulation of data collected from multiple sources [9-11], ensures that it is increasing worldwide, and not only among the elderly, but also in young [12,13], especially among disadvantaged individuals, affecting patients by increasing the burden of symptoms, the demand for care and treatment, as well as complicating their navigation through health systems, having become a consequence in a serious public health problem due to its negative repercussions on the quality of life, the greater tendency to disability and mortality, and the cost of using health services [14].

The care of people with multimorbidity falls largely on general practitioners (GPs), but daily practice is strongly influenced by a growing variety of individual protocols. The result is fragmented and poorly coordinated health services, potentially unsafe, and unnecessarily expensive and with a serious risk of yatrogenic polypharmacy [15,16], and these circumstances are not adequately addressed in professional training or research [17-19], and there is little evidence to suggest the best way to perform the care of these patients [20,21].

In addition, patients with a large accumulation of diseases have a secondary psychosocial problem "hidden": that of their own multimorbidity, both in their personal lives or in their interactions with the health system (they are frequent consultants, non-compliant, and they are "difficult" patients); the intensity and complexity of the problems can overwhelm even experienced professionals, produces feelings of bewilderment, despair, frustration and impotence in the GPs and the patient, and in many cases, the attention is entirely in somatic terms, which can "save patient, "but it also causes irreparable damage to him and his context [22].

On the other hand, it has been reported that there is a "power-law" phenomenon in health problems. Diseases are not uniformly distributed among the population of patients cared for in general medicine, but rather show a pattern of cumulative disadvantage; a small part of the population, practically 20%, accumulates almost 50% of bio-psycho-social problems. These problems seem to attract each other and to be added in the same people that suppose a small group of the population [23]. The challenge for future research is to confirm these clusters, and rule out that they are not due to chance. Longitudinal studies are required to explore the factors that produce or lead to multi-morbidity, and in particular to determine how in a person or family to which a first disease is diagnosed, others are added along the continuum of life, to allow the design of individualized preventive strategies [24]. Thus, there seem to be individuals or families 'in trouble', where historical events, life experiences, and formal and informal support may have led to be a "troubled family". And it has been suggested that focusing on these key individuals or families can achieve more impact, thus optimizing efforts [25].

Relationship between individual and population health is largely relative and dynamic. Their interrelated dynamism derives from a causally defined life course perspective on health determination starting from an individual's conception through growth, development and participation in the collective till death, all seen within the context of an adaptive society [26]. So, qualitative and quantitative longitudinal studies, in persons, families and populations, are needed to identify not only the types or patterns of diseases groupings - over what has been described a lot of literature-, but especially about the trajectory of the causal chain of accumulation of health problems in a power-law distribution where there are people, families and groups with cumulative disadvantage patterns [27]. In this scenario, multiple case studies, which pursue the development and contrast of certain explanations in a representative framework of a more general context, and aim to generate theory by contrasting the hypotheses within diverse contexts, can be especially useful [28].

In this context, the general objective of this study was to obtain new evidences or situations on which to base new theories about the accumulation of diseases in certain patients. Further, the study had two specific objectives: 1) to determine the prevailing hypothesis of cause of accumulation of health problems or diseases in "multiproblems" or "multimorbidity" patients; and 2) to determine the prevailing path, pattern or trajectory of those hypotheses of accumulation of diseases over time for these patients, in general medicine level, to assess their implications for decision-making.

Participants and Methods

Design and emplacement

A qualitative, longitudinal, descriptive, and retrospective case series study based on a single cohort was carried out. Analysis was based on a retrospective study of case records. For each case, the period in which the patient had been attended in a family medicine office in the Health Center Santa Maria de Benquerencia, Toledo, Spain, which has a list of 2,000 patients of both sexes over 14 years old was studied (In Spain GPs attend patients over 14 years old).

Design

The longitudinal study implied the existence of repeated measurements across follow-up; so, it can be considered a subtype of cohort study that allows inference to the subject level, to analyze changes in variables. The long duration of follow-up of some patients forced us to pay special attention to the control of the quality of the data over time and on quality control during data collection, to avoid information losses during follow-up and missing data in some measurements. During this period of time, was the same doctor in the office (who remains in the same consultation more than 25 years). Thus, he attended all patients, and used the same criteria (29). With the series of cases we try to find new evidences of a phenomenon, the formulation of new theory of reality; what is sought is to find the answers to questions in a scenario and given moment [30]. Study was qualitative, but when qualitative results were obtained, quantitative data were also obtained.

Sample, sample size, and inclusion criteria

The selection of the sample was informal (for convenience or available cases to which researcher had access), consisting of patients who the doctor remembered was presenting "multimorbidity" and who there were data in their clinical record to meet the criteria for entering the study [31,32]. Although the criteria of representativeness (probabilistic sample) were not followed to select the sample, a careful selection of the subjects was made following some characteristics specified in advance. This was continued, including new cases from the archive of medical records, when recalling any previous case, until the saturation of the data: when new clinical cases did not contribute new data to the previous ones.

The study had 2 criteria to include the cases:

1.Multimorbidity. It is usually the presence of two or more long term health conditions [33]; however, for our study, we wanted to see the pattern of accumulation of diseases, and with retrospective design, one the criteria for entering the study was "the presence of five or more long term health conditions at the time of obtaining the data, which could include:

-Physical and mental health pathologies

-Ongoing conditions such as learning disability

-Symptom complexes such as frailty or chronic pain

-Sensory impairment such as sight or hearing loss

-Alcohol and substance misuse

2. The second criterion was to have available his clinical data of the last five years.

Through the fulfilment of the exposed research criteria, it was intended to choose "typical" subjects that, although they do not meet the conditions of representativeness with respect to a population with similar characteristics, may instead offer the possibility of knowing in depth their situation. The criterion of the investigation advised a carefully chosen sample of convenience; thus, there is no representativeness of the resulting sample with respect to the total of elements that can participate (universe), but the phenomenon of accumulation of diseases in each case can be observed in depth [34]. The first cases were considered in epidemiological term as index cases, which means that beyond these the study should be expanded. So, a technique of snowball "mental" or "astute clinical observation" others patients attended previously were included until the saturation of the data [35].

Ethic aspects

No ethical approval was required for the study as this was part of a normal service with study of the diseases in the patient's medical records.

Analysis

From the medical record, other documents such as specialist reports, and physician-patient interview data, the cases were described in a short table or list of problems showing dates and the appearance of health problems or diseases. An analysis of the content of these lists of problems was carried out, to assign each health problem to a certain hypothesis of accumulation of diseases.

The following classification was used to code the different hypothesis of accumulation of diseases:

1. Causality, associations and linkages

2. Coincidences, seriality, or synchronicity

3. Concurrent (random or chance)

4. Iatrogenesis and complication

BOX 1: describes more thoroughly the definitions of the categories of the different hypothesis of accumulation of diseases.

In this way, by retrospectively reviewing the appearance of each health problem or disease in each patient, and by integrating the data of its clinical record and the memories that the doctor had about the interviews with patient and family, it was classified or codified each new health problem that was appearing in the evolution or vital trajectory of each case studied based on the classification of hypotheses of accumulation of diseases before exposed (BOX 1).

An analysis of the content of these lists of problems of each patient included was carried out, defining categories of hypotheses of accumulation of diseases, and carrying out this process of organizing qualitative data using Microsoft® Word [36,37].

The process was as follows: 1. The written transcripts of the lists of problems of the cases were read by the researcher, and categories were assigned to each of them; 2.-A new reading of the categories was made for each list of problems, re-assigning data to new categories, and thus forming a file of definitive categories; And finally, 3.-The results were interpreted and a generalization was drawn from these cases. Next, the sequences of disease development and the course followed were established, showing the order in the development of the problems for each case. Studying the beginning of different problems in each patient can be the starting point to identify the sequence of the development of that problem and can help decide how and when it is better to intervene to interrupt the chain of accumulation of diseases [38].

The period of follow-up of each patient was classified in 3 phases: Start, medium, and final, and data were obtained on the frequency of the different hypotheses of disease accumulation in each of these 3 periods. Subsequently quantitative data of number and % of the frequency of each of these mechanisms of accumulation of diseases in every case were obtained (39). The results were interpreted and a generalization was drawn from these cases.

Technique to control bias

1) The criterion of maximizing diversity in obtaining the sample was taken into account.

2) Triangulation:

-Methodological: data of a quantitative nature were combined with qualitative data (qualitative and quantitative was used as a technique to control the reliability and biases).

-Multiple sources for collecting evidence were used: Documentation, Interviews, and direct observations (28).

Gantt charts

Finally Gantt charts were drawn to visualize the pattern of disease accumulation over time in each patient, illustrating the start dates of the health problems.

Results

There were 18 cases, 9 men (age range: 39-89 years), and 9 women (age range: 31-76 years). From the cases 14-15, the

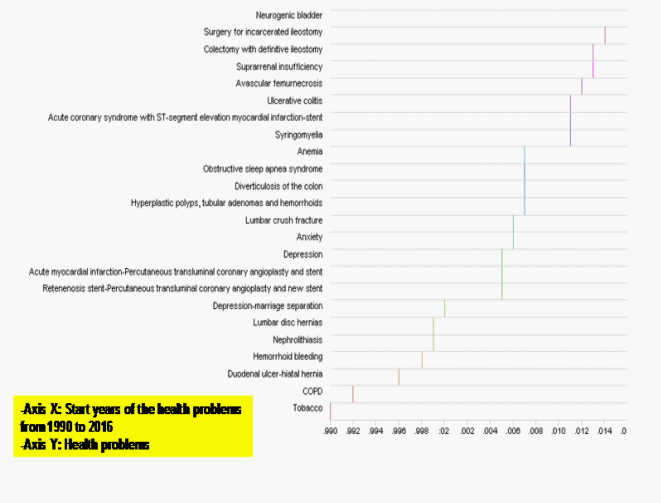

Figure 1: Grantt Chart Case 1

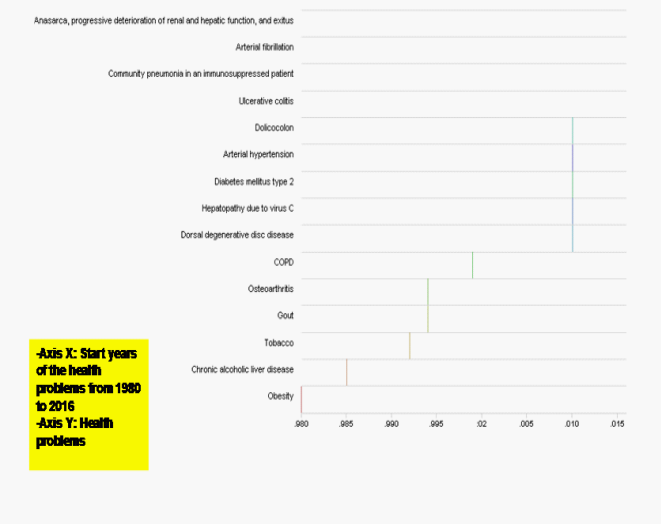

Figure 2: Grantt Chart Case 11

results were repeated (saturation) but for greater safety, up to 18 cases were included.

As an example, (Tables 1, 3, 5, and 7) present the qualitative data of 4 cases. For those same cases, as examples, (Tables 2, 4, 6, and 8) shows, the quantitative data of the frequencies of the different types of disease accumulation hypotheses that were considered plausible. Figures 1 to 4 show Gantt charts for these same cases, as examples, to illustrate the start date of the health problems.

Thus, we can see, for example, in Table 1, that exposes CASE 1, its accumulation of health problems according to the years and hypotheses of this accumulation. When analyzing the temporal trajectory it can be seen that in the first years mechanisms of common cause and corticovisceral predominate, in the middle stage there are cluster mechanisms, and in the final stage the mechanisms of complications predominate. Table 2 shows, for this same example of CASE 1, the quantitative data of the frequencies of the different types of disease accumulation hypotheses that were considered plausible. 45% of the accumulation is by Causality, associations and linkages, and 30% by Iatrogenesis or Complication. Figure 1 shows Gantt chart for this same CASE 1, and illustrate the start date of the health problems. In the second half of the period studied, the problems seem to accumulate more quickly (and correspond to complications of the previous ones).

Table 9 exposes the data of the 18 cases of the series. The accumulation of health problems occurs in the 63% of the time by Causality, associations and linkages (through a path of common origin, accumulation of risk factors or cluster, through genetic bases or molecular and biological linkages), in 22% by random or chance, in 11% by iatrogenesis and complication, and in 4% by coincidences, seriality or synchronicity.

Table 10 shows the frequencies of the disease accumulation hypothesis according to the period of time. In the trajectory of accumulation of diseases, causality, associations and linkages predominate in all phases (56% in the initial phase, 53% in the middle phase, and 61% in the final phase), the concurrent hypothesis (random or chance) predominate in the initial phases (44% in the initial phases of disease accumulation vs. 11% and 6% in the middle and final phases, respectively), and

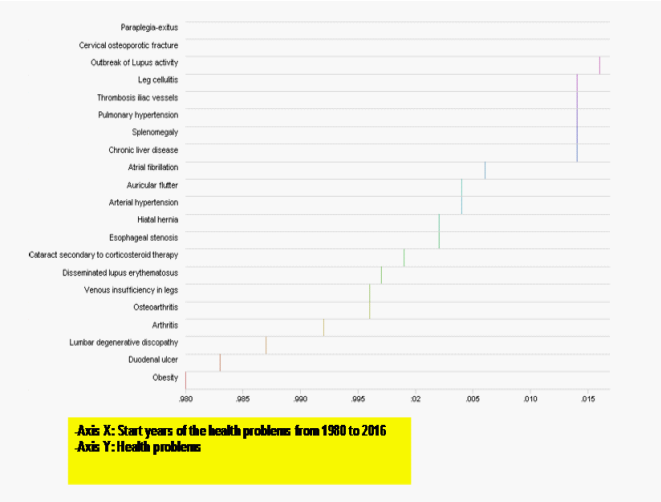

Figure 3: Grantt Chart Case 14

Table 1: Accumulation of health problems according to the years and hypotheses of this accumulation, in the case 1

Year	Hypothesis of Accumulation of Diseases	Health Problem
1990		Tobacco
1992	Common cause (pathophysiology)	COPD
1996	Common cause (pathophysiology)	Duodenal ulcer-hiatal hernia
1998	Concurrent (random or Chance)	Hemorrhoid bleeding
1999	Concurrent (random or Chance)	Nephrolithiasis
1999	Concurrent (random or Chance)	Lumbar disc hernias
2000	Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	Depression-marriage separation
2005	Through the accumulation of risk factors	Acute myocardial infarction-Percutaneous transluminal coronary angioplasty and stent
2005	Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	Depression
2005	Cluster	Restenosis stent-Percutaneous transluminal coronary angioplasty and new stent
2006	Complication	Lumbar crush fracture
2006	Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	Anxiety
2007	Complication	Anemia
2007	Concurrent (random or Chance)	Hyperplastic polyps, tubular adenomas and hemorrhoids
2007	Coincidences, Seriality, Synchronicity	Diverticulosis of the colon
2007	Common cause (pathophysiology)	Obstructive sleep apnea syndrome
2011	Coincidences, Seriality, Synchronicity	Syringomyelia
2011	Cluster	Acute coronary syndrome with ST-segment elevation myocardial infarction-stent
2011	Molecular and biological linkages	Ulcerative colitis
2012	Complication	Avascular femurnecrosis
2013	Complication	Suprarrenal insufficiency
2013	Complication	Colectomy with definitive ileostomy
2014	Complication	Surgery for incarcerated ileostomy
2016	Complication	Neurogenic bladder

Table 2: For the Example of Case 1, Quantitative Data of The Frequencies of The Different Types of Hypothesis of Accumulation of Diseases That Considered Plausible

Classification of the Different Hypothesis of Accumulation of Diseases	No. (%)
1.-Causality, associations and linkages:	10 (44%)
1.1.) Through a path of common origin	6 (26%)
1.1.1.) Common cause (pathophysiology)	3 (13%)
1.1.2.) Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	3 (13%)
1.2) Accumulation or Cluster	3 (13%)
1.3) Through genetic bases or molecular and biological linkages	1 (5%)
2.-Coincidences, Seriality, Synchronicity	2 (9%)
3.-Concurrent (Random or Chance).	4 (17%)
4.-Iatrogenesis or Complication	7 (30%)
TOTAL	23(100%)

Table 3: Accumulation of Health Problems according to the Years and Hypotheses of this Accumulation, in the Case 11

Year	Hypothesis Of Accumulation Of Diseases	Health Problem
1980		Obesity
1985	1.1.1.) Common cause (pathophysiology	Chronic alcoholic liver disease
1992	1.1.2.) Through a córtico-visceral or psychosomatic or holistic or psychosomatic pathway	Tobacco
1994	1.2.1.) Through the accumulation of risk factors	Gout
1994	1.2.1.) Through the accumulation of risk factors	Osteoarthritis
1999	1.1.1.) Common cause (pathophysiology	COPD
2010	1.2.1.) Through the accumulation of risk factors	Diabetes mellitas type 2
2010	Common cause (pathophysiology	Dolicocolon
2010	1.2.1.) Through the accumulation of risk factors	Dorsal degenerative disc disease
2010	2.-Coincidences, Seriality, Synchronicity	Hepatopathy due to virus C
2010	1.2.2.) Cluster	Arterial hypertension
2016	1.4) molecular and biological linkages	Ulcerative colitis
2016	4.2.) Complication	Community pneumonia in an immunosuppressed patient
2016	1.1.2.) Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	Arterial fibrillation
2016	4.2.) Complication	Anasarca, progressive deterioration of renal and hepatic function

Table 4: For the Example of Case 11, Quantitative Data of the Frequencies of the Different Types of Hypothesis of Accumulation of Diseases that Considered Plausible

Clasificación De Las Diferentes Hypothesis Of Accumulation Of Diseases	No. (%)
1.-Causality, associations and linkages:	11 (79%)
1.1.) Through a path of common origin	5 (36%)
1.1.1.) Common cause (pathophysiology)	3 (21%)
1.1.2.) Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	2 (14%)
1.2) Accumulation or Cluster	5 (36%)
1.3) Through genetic bases or molecular and biological linkages	1 (7%)
2.-Coincidences, Seriality, Synchronicity	1 (7%)
3.-Concurrent (Random or Chance).	0
4.-Iatrogenesis or Complication	2 (14%)
TOTAL	14 (100%)

Table 5: Accumulation of health problems according to the years and hypotheses of this accumulation, in the case 14

Year	Hypothesis of Accumulation of Diseases	Health Problem
1980		Obesity
1983	1.3) Through genetic bases	Duodenal ulcer
1987	1.2) Accumulation	Lumbar degenerative discopathy
1992	1.3) Through genetic bases	Arthritis
1996	1.2) Accumulation	Osteoarthritis
1996	1.2) Accumulation	Venous insufficiency in legs
1997	1.1.1.) Common cause (pathophysiology	Disseminated lupus erythematosus
1999	4.- Iatrogenesis and Complication	Cataract secondary to corticosteroid therapy
2002	1.3) Through genetic bases	Esophageal stenosis
2002	1.2) Accumulation	Hiatal hernia
2004	1.2) Accumulation	Auricular flutter
2004	1.2) Accumulation	Arterial hypertension
2006	1.1.1.) Common cause (pathophysiology	Atrial fibrillation
2014	1.1.1.) Common cause (pathophysiology	Chronic liver disease
2014	1.1.1.) Common cause (pathophysiology:	Splenomegaly
2014	1.1.1.) Common cause (pathophysiology	Pulmonary hypertension
2014	1.1.1.) Common cause (pathophysiology	Thrombosis iliac vessels
2014	1.1.1.) Common cause (pathophysiology	Leg cellulitis
2016	1.1.2.) Through a cortical-visceral or psychosomatic	Outbreak of Lupus activity
2017	4.- Iatrogenesis and Complication	Cervical osteoporotic fracture
2017	1.2) Accumulation	Paraplegia

Table 6: For the example of case 14, quantitative data of the frequencies of the different types of hypothesis of accumulation of diseases that considered plausible

Clasificación De Las Diferentes Hypothesis of Accumulation of Diseases	No. (%)
1.-Causality, associations and linkages:	18 (90%)
1.1.) Through a path of common origin	7 (35%)
1.1.1.) Common cause (pathophysiology)	7 (35%)
1.1.2.) Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	0
1.2) Accumulation or Cluster	8 (40%)
1.3) Through genetic bases or molecular and biological linkages	3 (15%)
2.-Coincidences, Seriality, Synchronicity	0
3.-Concurrent (Random or Chance).	0
4.-Iatrogenesis or Complication	2 (10%)
TOTAL	20 (100%)

Table 7: Accumulation of health problems according to the years and hypotheses of this accumulation, in the case 18

Year	hypothesis of accumulation of diseases	Health Problem
1980		Cervical cancer surgery
1992	3.-Concurrent (random or chance)	Obesity
1992	3.-Concurrent (random or chance)	Tobacco
1993	1.2.1.) Through the accumulation of risk factors	Lumbar disc hernia surgery
1994	3.-Concurrent (random or chance)	Menopause
1995	1.3) Through genetic bases	Thrombopenia
1996	1.1.2.) Through a cortical-visceral or psychosomatic	Asthenia, headache and chronic dizziness
1996	1.1.2.) Through a cortical-visceral or psychosomatic	Musculoskeletal pain
1997	1.1.2.) Through a cortical-visceral or psychosomatic	Chronic insomnia
1999	3.-Concurrent (random or chance	Myopia
2001	2.-Coincidences, Seriality, Synchronicity	Fibromyalgia
2002	1.1.2.) Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	Tension headache
2002	3.-Concurrent (random or chance	Kidney Colic
2004	3.-Concurrent (random or chance	Hallux valgus
2005	1.1.1.) Common cause (pathophysiology	Osteopenia
2005	1.3) Through genetic bases	Chondrocalcinosis
2006	1.3) Through genetic bases	Osteoarthritis
2006	1.2) Accumulation	Lumbar degenerative discopathy
2007	1.1.2.) Through a cortical-visceral or psychosomatic	Generalized chronic pain
2008	1.2) Accumulation	Polyarthrosis
2011	1.1.2.) Through a cortical-visceral or psychosomatic	Arterial hypertension
2013	4.- Iatrogenesis and Complication	Cavernoma cerebral found coincidentally
2014	1.1.1.) Common cause (pathophysiology	Cervical herniated discs
2014	1.2) Accumulation	Intestinal obstruction-exploratory lapatomy
2014	4.- Iatrogenesis and Complication	Sepsis
2014	4.- Iatrogenesis and Complication	Spinal pyomyosis
2014	1.2) Accumulation	Atrial fibrillation
2014	1.1.2.) Through a cortical-visceral or psychosomatic	Anxiety-Depression
2015	1.2) Accumulation	Thalamic hematoma and exitus

Table 8: For the example of case 18, quantitative data of the frequencies of the different types of hypothesis of accumulation of diseases that considered plausible

Clasificación De Las Diferentes Hypothesis of Accumulation of Diseases	No. (%)
1.-Causality, associations and linkages:	18 (64%)
1.1.) Through a path of common origin	9(32%)
1.1.1.) Common cause (pathophysiology)	2 (7%)
1.1.2.) Through a cortical-visceral or psychosomatic or holistic or psychosomatic pathway	7 (25%)
1.2) Accumulation or Cluster	6 (21%)
1.3) Through genetic bases or molecular and biological linkages	3 (11%)
2.-Coincidences, Seriality, Synchronicity	1 (4%)
3.-Concurrent (Random or Chance).	6 (21%)
4.-Iatrogenesis or Complication	3 (11%)
TOTAL	28 (100%)

Table 9: The quantitative data of the 18 cases of the series

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16	Case 17	Case 18	
AGE (Years)	61	59	39	31	47	40	55	70	56	43	69	71	89	68	53	67	76	67	TOTAL
Sex	Male	Woman	Male	Woman	Woman	Woman	Male	Woman	Male	Woman	Male	Male	Male	Male	Woman	Male	Woman	Woman	
Clasificación De Las Diferentes Hypothesis Of Accumulation Of Diseases	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
1.-Causality, associations and linkages:	10 (44%)	11 (58%)	9 (82%)	10 (53%)	14 (67%)	8 (80%)	15 (71%)	19 (65%)	20 (83%)	15 (83%)	11 (79%)	21 (75%)	18 (45%)	18 (90%)	8 (38%)	14 (50%)	15 (54%)	18 (64%)	254 (63%)
2.-Coincidences, Seriality, Synchronicity	2 (9%)	1 (5%)	0	1 (5%)	4 (19%)	1 (10%)	1 (5%)	0	0	1 (6%)	1 (7%)	0	1 (2%)	0	0	0	1 (4%)	1 (4%)	15 (4%)
3.-Concurrent (random or Chance).	4 (17%)	7 (37%)	2 (185)	4 (21%)	0	1 (10&)	2 (10%)	4 (14%)	4 (17%)	2 (11%)	0	6 (21%)	10 (25%)	0	13 (62%)	13 (46%)	11 (39%)	6 (21%)	89 (22%)
4.-Iatrogenesis or Complication	7 (30%)	0	0	4 (21%)	3 (14%)	0	3 (14%)	6 (21%)	0	0	2 (14%)	1 (4%)	11 (28%)	2 (10%)	0	1 (4%)	1 (3%)	3 (11%)	44 (11%)
Total Accumulation Of Diseases	23 (100%)	19 (100%)	11 (100%)	19 (100%)	21 (100%)	10 (100%)	21 (100%)	29 (100%)	24 (100%)	18 (100%)	14 (100%)	28 (100%)	40 (100%)	20 (100%)	21 (100%)	28 (100%)	28 (100%)	28 (100%)	402 (100%)

Table 10: Frequencies of the hypothesis of accumulation of diseases according to the period of time

Classification of The Different Hypothesis of Accumulation of Diseases	Initial Period No. (%)	Middle Period No. (%)	Final Period No. (%)
1.- Causality, associations and linkages:	10 (56%)	15 (83%)	11 (61%)
2.-Coincidences, Seriality, Synchronicity	0	0	0
3.-Concurrent (random or Chance).	8 (44%)	2 (11%)	1 (6%)
4.-Iatrogenesis or Complication	0	1 (6%)	6 (33%)
TOTAL CASES	18 (100%)	18 (100%)	18 (100%)

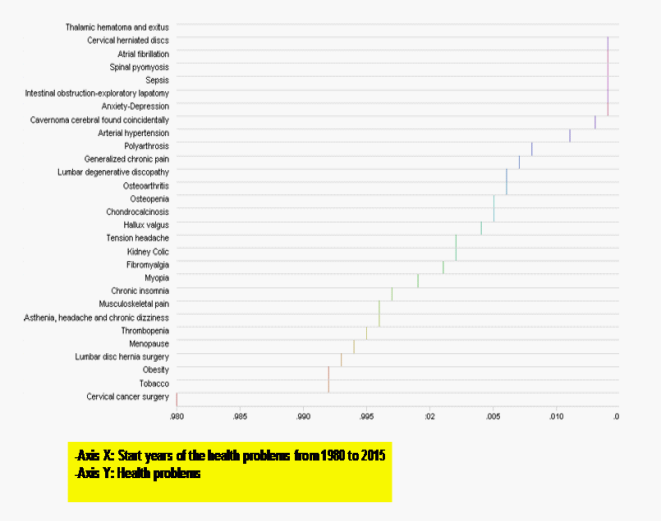

Figure 4: Grantt Chart Case 18

iatrogenesis and complication predominates in the final phases (33% in the final phases vs. 0, and 6% in the initial and middle phases).

Discussion

Hypothesis of accumulation of diseases

Increasing numbers of people are found to have two or more diseases at the same time, which is termed multimorbidity. Great heterogeneity has been described in multimorbidity, and many studies have attempted to reduce it by identifying clusters of multimorbid or combinations of disease [14, 23,33,40,41]. Thus, clusters of health problems have been described - which sometimes have been called "community syndromes" [42-44]. The accumulation of health problems are a complex condition and may occur as a result of genetic predisposition (a natural tendency), environmental or unknown factors. Several multimorbidity clinical patterns had been described: 1) cardiometabolic, 2) mechanical / obesity / thyroid, 3) psychiatric / substance abuse, 4) depressive, 5) psychogeriatric [45]. Also, several patterns or types of multimorbidity have been hypothesized: Concurrent (random), Cluster (eg. hypertension, coronary artery disease, and diabetes mellitus), Common cause (pathophysiology), Complication (temporal relationship), etc. BOX 1 presents an attempt to integrate the different hypotheses of disease accumulation. Although knowledge of these disease clusters may theoretically help for a useful approach to how to address comorbidity, however, the internal structure of multimorbital clusters and the linkage between combinations of diseases and clusters are still unknown [23,40,45-54].

In our study, the coding of the mechanism of accumulation of each new disease in the cases studied was based on a set (or triangulation) of data: the clinical and personal experience of the physician that allowed to combine quantitative data with qualitative data, the evidences obtained by the longitudinal and transversal data of each case, the plausibility of each hypothesis in each context, and the data previously published in the bibliography [28]. And our results basically coincide with the known or intuited [55]: the mechanism due to causality, associations and linkages, where there is a striking connection between coincident and concurrent factors in space and time (basically consisting of the space-time succession of cause and effect), accounts for more than half of the reasons for accumulation of diseases, and another more than 10% of causes were due to the mechanism by iatrogenesis and complication (due to our own interventions to solve other previous problems, such as pharmacological iatrogenesis or surgical sequelae, with a temporal relationship between medical intervention and new disease or complication); that is, a frequency although intuited, not previously accepted in this amount. Both mechanisms are susceptible to being prevented, so another important result of the study is that the presence of multimorbidity is not a natural and forced consequence of nature, and that it can be in a small part bur significant, self-created by the own medical intervention.

On the other hand, in our study it is observed that the causes due to coincidences, seriality, or synchronicity (a non-causal non-physical principle active in nature; the simultaneous occurrence of two significant events that are not causally connected; a relationship that can not be explained by the principle of cause and effect, but that nevertheless makes sense for the observer), and concurrent (random or chance), are infrequent causes of the accumulation of diseases.

Longitudinal studies are required to explore the factors that lead to the accumulation of diseases in certain people

Longitudinal studies are required to explore the factors that produce or lead to the accumulation of diseases and to the multi-morbidity, and in particular to determine how in a person or family to which a first disease is diagnosed, others are added along the existential continuum of life, to allow the design of individualized preventive strategies [24]. This study responds

to this need. A longitudinal study or follow-up study implies the existence of repeated measurements across follow-up. According to these ideas, these studies can be considered a subtype of cohort study that, in contrast with life-table cohort studies, allows inference to the subject level, to analyze changes in variables and transitions among different health states. This can be done prospectively or retrospectively, and the study can be observation or intervention. Our study, carried out retrospectively, has the strong point that it was the same doctor and with the same criteria that he attended during all the years studied to the patients, so he has a great "clinical experience" in relation to the cases studied [29].

Multiple case studies aim to generate theory

Multiple case studies aim to generate theory by contrasting the hypotheses extracted within diverse contexts. Thus, our study pursued the development and contrasts of certain explanations in a representative framework of a more general context; that is, generate theory by contrasting hypotheses [28]. Our results in the study of the natural history of the accumulation of diseases, propose a new theory: the multimorbidity in a small but significant part is created by the medical intervention itself. Although it is not an entirely new idea, with this series case study new evidences are found about this phenomenon, so that this new theory of reality can be formulated in the context of patients with accumulation of diseases or multimorbidity in family medicine, and allows us finding answers to questions about preventing the accumulation of health problems in their real-life context.

One of the main biases associated with case studies is that their conclusions are not statistically generalizable [56]. However, what can be generalized are the theoretical propositions, since the objective of the researcher is to understand the interaction between the different parts of a system and the important characteristics of the system, in such a way that the analysis carried out can be applied a generic way, expanding and generalizing theories-analytical generalization-and not enumerating frequencies-statistical generalization. In any case, the case study methodology is not synonymous with qualitative research, since case studies can be based on any combination of quantitative and qualitative evidence [30,57, and 58]. In our study, after the qualitative data, we obtained quantitative data of number and% of the frequency of each of these mechanisms of accumulation of diseases.

A sample with typical cases of accumulation of diseases over time

In our study the selection of the sample was for convenience: the available cases to which the researcher had access. That is, although the criteria for representativeness (probabilistic sample) were not followed to select the sample, a careful selection of the subjects was made following the characteristics specified in advance, and thus choosing "typical" cases that the possibility of knowing in depth their situation [34]. This can be seen by looking at Tables 1, 3, 5, and 7, and Figures 1 to 4, which present the qualitative data of 4 cases as examples.

Study limitations

Design: Our study necessarily has the limitations imposed by its qualitative design, of series of case study, and retrospective. But the criterion of maximizing diversity in obtaining the sample was followed, and the saturation to decide its size. Also, a careful choice of subjects was made following characteristics specified in advance.

Codification: For the codification of the different hypotheses of accumulation of diseases for each new disease in each case, were used the knowledge of the doctor who attended the patient, from various sources, and the data of the bibliography; However, it was difficult, because basically, the internal structure of multimorbidity clusters and the linkage between combinations of diseases and clusters are still unknown [41,49].

This difficulty was greater in the codification of "coincidences, seriality, or synchronicity [53,54], since the synchronicities are very personal: they are significant for those who experience them, but not for those around them. A synchronic phenomenon is a coincidence that holds a special meaning for those who live it, but that may be totally irrelevant to others. Thus, since the researcher was not in the patient's mind, it was necessary to judge based on what was heard in the continuous interviews with the patient and his family, what was seen or imagined that the patient could think of. For example, a patient had said at one point to the doctor: "I have dreamed that I will have Fibromyalgia"; and indeed years later that diagnosis was made (CASE 18). Another patient before the doctor's proposal to investigate more thoroughly with the hepatologist his chronic alcoholic liver disease, had said: "I feel perfectly well ... In the

consultation or tests I will be able to catch a virus"; and a few years later he was diagnosed with hepatopathy due to virus C (CASE 11). But, despite the care that was taken, it cannot be completely verified.

Conclusions

Our study finds 5 main results: 1) the mechanism due to causality, associations and linkages supposes more than half of the reasons of accumulation of diseases, and the mechanism by iatrogenesis and complication supposes other 10% of causes of accumulation of diseases; 2) both mechanisms are susceptible to being prevented, so another important result of the study is that the presence of multimorbidity is not a natural and forced consequence of nature; 3) the causes due to coincidences, seriality, or synchronicity, and concurrent (random or chance), are less frequent or infrequent causes of the accumulation of diseases; 4) the accumulation of diseases or multimorbidity in certain people can be in a phenomenon, in a small but significant part, self-created by the medical intervention itself; and 5) the accumulation of health problems can be prevented, on the one hand by acting on the mechanisms of Causality, associations and linkages, which occur in the patient's initial phases, but mainly avoiding Iatrogenesis and Complication, which occurs in the final phase of the pathobiography, which It could eliminate more than 10% of accumulated health problems in patients with morbidity.

A new theory about the accumulation of diseases is proposed: the multimorbidity can be, in an small but important and significant part, created by the medical intervention itself. From the dominant biomedical point of view it may seem at first sight an unlikely theory, but if we follow the precepts or methods of Sherlock Homes, "when you have eliminated the impossible whatever remains, however improbable, must be the truth.

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