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A Heuristic Model of Primary Brain Cancers and Serious Mental Illnesses, etc., Supporting the Idea of Different Clinical Expressions with Aging of the Same Epigenetic Factors

Ilir **Akshija***

[1]Tirana Univeristy Hospital Center 'Mother Teresa', Rruga e Dibrës, Tiranë, Albania.

ABSTRACT

Introduction: Combined epidemiological hospital data on primary brain diagnoses; primary brain cancers and serious mental illnesses, etc., of the age on first admission are suggestive of common epigenetic factors, among others. We propose a heuristic model combining age distributions of both entities which show patterns of a composed normal distribution supporting the idea of different clinical expressions with aging of the same epigenetic factors.

Methods: Retrospective data from Electronic Patients Records (EPR), TUHC "Mother Teresa", Albania, years 2005-2021, were analyzed after creating cutoffs on age, county (capital), first admission and diagnosis groups. Combination of age at first hospitalization for the main groups of diagnoses was tested for normality, hypothesized to be a composed normal distribution.

Results: The total number of patients for the period 2005-2021, was 48,303 admissions. First admissions were N=31,603 (65.4%), of which N=15,896 (50.3%) were from Tirana (the capital) county. The number of first admissions for the two main categories 'Mental Disorders' and 'Other' for Tirana (the capital) county were respectively; 6,807 (42.8%) and 9,089 (57.2%). Age on first admission mean (median) for Tirana county was 35.1 ± 22.1 (36.0) years. Age on first admission, mean (median), for the two categories for Tirana county were respectively; 37.7 ± 15.4 (37.2) years and 33.0 ± 26.3 (31.0) years and split by sex; male (36.2 ± 15.4 (35.3) years and 32.4 ± 26.4 (28.0) years, p<0.001) and female (39.4 ± 15.4 (39.6) years and 33.8 ± 33.0 (26.0) years, p<0.019). Age-specific distribution (> 15years) data on 'Mental Disorders', 'Other' and 'Total' for Tirana county test positive about normality, Shapiro-Wilk > 0.005 but data for 'mental disorders' don't pass the ''95% range check''.

Conclusion: Independent and common factors of brain cancers and serious mental illnesses, etc., show patterns of a composed normal distribution at the age of first hospitalization.

Key words: Primary brain diagnoses; Serious mental illness; Brain cancers;Normal distribution; Epigenetic

*Corresponding Author:
ilir.akshija@yahoo.com

INTRODUCTION

Tanycytoma, is a suggestion to name Pylomyxoid astrocytoma's, one of the glial brain tumors. The term originates from the name of precursor cells found in the third ventricles floor and inside circumventricular organs. Thus, the trend of tumor classification tends to reflect the cell origin which questions the traditional mature cell degeneration theory.[1] Not only, the same tumor developing in the same patient is subject of grading. During an early phase it can be considered as low-grade but later progressing to higher grades, its aggressiveness determines malignancy, as is the case of diffusely infiltrating grade II astrocytomas.[2] Thus the patient's diagnosis changes over time with repercussions on coding, or the time of diagnosis determines grading, or the classification itself evolves. Grading, associated with histopathological diagnosis and molecular genetics projects a satisfactory layered diagnosis.[3] But, statistically approaching the subject remains very challenging. Whatever the developments, the taxonomy of the functional brain still uses anatomical terminology.[4] A recapitulation on gliomas origin, which make somewhat as 80% of the malignant cases, supports that they exhibit characteristics of glial cells, mainly precursors of Neural Stem Cells (NSCs) and oligodendrocytes, accompanied with the absence or presence of genetic mutations, and unclear for neural mature cells.[5-7] The anatomical structure of the brain and the brain physiology itself is subject and object of its functions. The situation is also of high complexity when it comes to mental disorders. Numerous studies support the old idea that the structure of the brain is shaped by experience. At least the damage of the brain from stress is accepted on global research agenda. The hypothesis of the neurodevelopmental model of schizophrenia goes along with the common occurrence of trauma in psychotic individuals.[8] Psychosis as an occurrence on psychotic spectrum disorder can be found in approximately 3% of the population.[9] Biological factors of psychosis are mixed with psychological and social factor, while Primary Malignant Neoplasm of Brain are prone to at least biological factors which may or may not be common with psychosis. The idea of psychological and social factor promoting mechanism initiating brain neoplasia requires research support. On the psychosis side, courageous ideas as Laing (1972) which considers psychosis a healthy reaction to a mad society went further supported from Goffman (1961) and Szasz (1974) emphasizing that politics stands between psychosis and society.[10] The overlap of experiences, psychotic and spiritual, would suggest a form of revolt without involvement in politics.

Although International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) can be used concomitantly for different purposes the DSM-5 altering to search for cultural variables can be conflicting with the ICD-10 approach in this topic. The ICD-10 suggestion was considered even misleading because culture-specific disorder's decreased frequency doesn't exclude their screening.[11] Sometimes extreme ambient factors are present with specific behavioral anomalies which someone considers a disorders and other as an extreme adaption to stress. The ICD-11 version of International Classification of Diseases tended to be more similar to DSM-5, for example both don't emphasize first-rank symptoms, diversely from ICD-10 which does the opposite.[12] Classification means diagnosis, and treatment but also social stigma, financial issues and different expected outcomes. These categorizations bring a high burden but are at the same time a richness of human diversity. New classifications and/or categorizations are forward-

ed not only for the purpose of diagnostics, treatment or medical billing but serve also the reverse, to find the roots of specific diseases from data we already dispose. Primary brain tumors involve tumors originating from and beyond brain cells, including meninges, etc. Confining to brain tumors starting in the brain cells we can create a search keyword expanding to other diagnoses supposed to originate on cells inside the brain, basically the term diagnoses affecting the brain originating from neuroblasts, or primary brain diagnoses. Mental disorders are the major group, followed by hereditary and degenerative brain disorders, epilepsy and multiple sclerosis. These diagnoses are core to major groups in terms of frequency and disability which would fulfil the above criterion of confinement, and formulated as primary brain diagnoses.

This regrouping, based on common origins, primary brain diagnoses, stemming in different diagnosis, expressing similarities, one of the major ones is psychosis, spins toward a heuristic model organizing these patterns and arising the question of common epigenetic factors and determining their different outcomes as different diagnoses through aging.

Many phenomena in medical sciences are a combination of two or more elements with different distributions. SARS-CoV-2 immune response is a good example of a combination of IgM antibodies peaking, followed by later IgG peaking and specific T and B cells memory cells resulting even after disappearance of serum antibodies.[13] What we actually dispose are diagnoses and age at first admission. Thus age distribution of first admissions is considered an important benchmark of disease development as a symptomatic expression requiring specialized care, which is different from age of onset but important for qualitative treatment changes and prognosis. Age at first admission becomes a useful clinical marker recognizing the indispensability of specialized medical care. To construct a hypothesis amassing a spectrum of diagnoses including brain tumors and psychotic disorders assuming that there are common, including socio-environmental, risk factors we must expect projected reflections of the same cause on both subject which is also expected to be blurred from other factors. Thus only mature subjects were included assuming only the exposure to socio-environmental factors acting in legally responsible persons. American Academy of Pediatrics extends adolescence to 21 years, but the middle group ranges from 15–17 years.[14] By definition epilepsy is a chronic brain disease but without a documented cause in about 50% of the cases. Epilepsy predominate in the age-group less than 1 year of age which is well documented in hospital admissions and in the elderly which is not well documented.[15] The data become fuzzy on terms of etiology and frequency making this nosology prone to exclusion because of the guaranteed expected bias towards study goals. The favorable long-term outcomes especially for pediatric patients make epilepsy relatively lessening in its burden but important cause of disability and mortality.[16]

METHODS

The distribution patterns on age at first hospitalization for primary brain cancers and serious mental illnesses, etc., were further scrutinized through superposing the data from both entities and searching for further patterns synthetized as a heuristic model.

The study methodology is based in constructing cutoffs. Cutoffs were created for age, county (capital), epilepsy, first admission and diagnosis groups. All these definitions were considered subject of cutoffs, built in thy study's presumption or necessity. Electronic Patients Records (EPR) from Tirana University Hospital Center "Mother Teresa", Albania were retrieved from the digital hospital repository of the patients' records, years 2005-2021. The hospital setting serves as a tertiary structure for the whole country and as a secondary and tertiary structure for the county of Tirana. Definition of cases and inclusion and exclusion criteria is realized using ICD-9 (International Classification of Diseases, Ninth Revision), three-digit code[17] Inclusion criteria of ICD-9 codes was based in the principle of 'primary brain disease'.

Every Electronic Patients Record (EPR) records next to the ICD-9 code, as free text, what the curing physician registers by handwriting as the final diagnosis on discharge. This text is used to definitely include or exclude a patient from the study when considered a doubtful case.

Cases represent hospital admissions, which consecutively counts patients accessing the hospital, rendering it a purposive sample. We presume the majority of tumor cases are admitted at least once.

Form the ICD-9 three-digit code of the Tabular List of Diseases chapters on; 1. NEOPLASMS (140-239), 2. MENTAL, BEHAVIORAL AND NEURODEVELOPMENTAL DISORDERS (290-319) and 3. DISEASES OF THE NERVOUS SYSTEM AND SENSE ORGANS (320-389) were primarily included for further evaluation.

For 'Neoplasms' were chosen codes; 191 - Malignant neoplasm of brain, 192 - Malignant neoplasm of other and unspecified parts of nervous system were excluded, including code 192.1 - Malignant neoplasm of cerebral meninges, Benign neoplasm of brain and other parts of nervous system – 225, including only code 225.0 – Brain, and excluding others, including Benign neoplasm of cerebral meninges 225.2. All were aggregated as Neoplasms (140-239).

For 'Mental, behavioral and neurodevelopmental disorders' codes from 290 to 319, excluding codes 291, 292, 293, 294, 304, 305. All were aggregated as groups; Organic psychotic conditions (290–294), Other psychoses (295–299), Neurotic disorders, personality disorders, and other nonpsychotic mental disorders (300–316) and Mental retardation (317 - 319). Psychoses (290-299) Other mental disorders (300-319).

For 'Diseases of the nervous system and sense organs' codes from Group 2, Hereditary and degenerative diseases of the central nervous system (330-337). Code 334 - Spinocerebellar disease was included/excluded case by case because of the conditions cause in relation to brain, for example ataxia caused from multiple sclerosis vs. medication. The same was applied for codes 335, 336 and 337, and codes from Group 3, Other disorders of the central nervous system (340-349). Code 340 - Multiple sclerosis was included, other codes 341-349 were subject of inclusion/exclusion case by case. Code 345 – Epilepsy was included and later it was split from main analysis because of epilepsy etiology especially in relation to the population study criteria. All were aggregated as Hereditary and degenerative diseases of the central nervous system (330-337) and Other disorders of the central

nervous system (340-349). Data come from an exhaustive database and the excluded cases result from the principal inclusion criterion, primary brain diagnoses, thus data can be considered complete and there are no missing data.

Tirana county was chosen as the catchment area because its historical population is known and especially patients diagnosed with malignant brain tumors are at least once admitted in this institution for diagnosis, treatment or medical billing procedures. INSTAT Albania censuses 2011 and 2023 population registrations were used to calculate crude rates.[18-19] The important epidemiological question; 'whether the number of psychiatric patients contacting healthcare settings are representative of the population?' is affirmative for diagnoses associated with psychosis in developed countries and negative for depression and anxiety in general.[20]

A cutoff on maturation (age) was taken as a compromise because of worldly variation. The age of 15 years, an approximation of UN Convention on the Rights of the Child (2007) on MACR (minimum age of criminal responsibility), encouraged a range of around 14 to 16 years, and the American Academy of Pediatrics suggests a range of 15–17 years.[14, 21]

The age of onset it is also a cutoff in itself. It can be considered as patients' epidemiological viewpoint because generally the onset of a disease is first perceived from the patient or close family and friends. The age of onset is strongly related to the number of cases, disability and life expectancy. Bringing all cases in one line, age of onset, even for apparently unrelated diagnoses makes sense. Four theoretical patients diagnosed with 'C71 Malignant neoplasm of brain' are lined beside four theoretical patients diagnosed with Schizophrenia, schizotypal and delusional disorders (F20–F29) (Figure 1). A patient can be born with a condition or never have it, the patient can spend a long time without the condition or with it. Age of onset brings all patients on the same line. This is time 0.

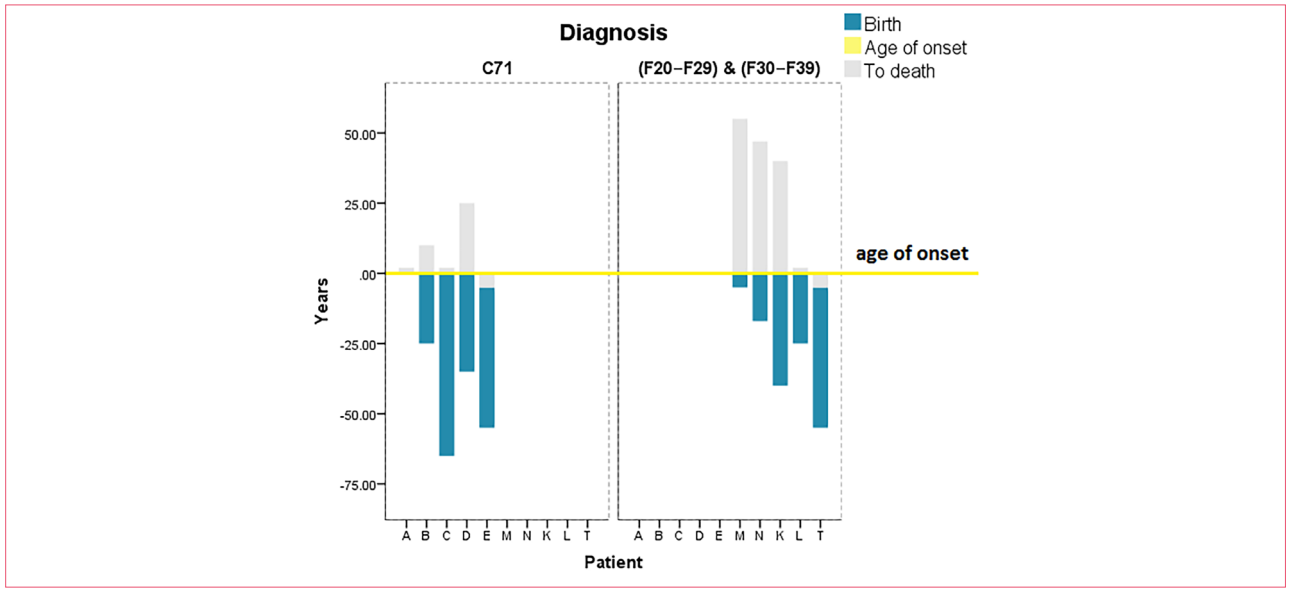

Figure 1. Example of age of onset for, Malignant neoplasm of brain (C71) and Schizophrenia, schizotypal and delusional disorders (F20–F29), ICD-10 codes. (Appendix A)

A- Congenital brain tumor (CBTs), B- Good survival outcome, C- Poor survival outcome, D- Very good survival outcome, E- C71 free, M- Autistic disorder, N- The usual development form, K- Late onset, L- Suicide, T- (F20–F29) & (F30–F39) free.

Although the same epigenetic factors can act through all age-groups, their perception and behavioral reaction depend on the maturity level. Brain tumors start to rise again after the above maturity cutoff, legally recognized, and schizophrenia cases sharply arise at the same time. On the other hand, the presupposed socio-economic epigenetic factors require the minimum of maturity to get in effect or at least to create two sets of age-groups of response towards them. This suffices to exclude younger age-groups as study targets.

The hospital admission is a medical decision taking an administrative form for the management of a certain health condition in need of a special service.[22] Thus the health condition exceeds all other possibilities and the decision maker judges that the patient needs to enter the health care facility. Thus, a condition not possible to be treated in ambulatory ground is admitted. Age of first admission becomes an important cutoff.

When testing for normality Kolmogorov–Smirnov test was used for the large dataset of age distribution, while the Shapiro–Wilk test is used for data categorized as age-groups, after transformation as crude rates. Age-groups were constructed second INSTAT, Albania. Age-specific standardization was performed. Z (Z = Skew value / SE skewness) value (the critical ratio); skewness and kurtosis are used to support normality of distributed values. A last calculation was the ‘‘95% range check’’, which evaluates if the range ($\bar{x} \pm 2$ SD) extends below 0, suggesting original data skewness. Analysis was performed through the IBM® SPSS® Statistics 26 software.

RESULTS

The total number of patients fulfilling selection criteria for the seventeen years’ period 2005-2021, was 48,303 admissions. First admissions were N=31,603 (65.4%), of which N=15,896 (50.3%) were from Tirana (the capital) county. The number of first admissions for the two major categories ‘Mental Disorders’ and ‘Other’ were respectively; 11,731 (37.1%) and 19,872 (62.9%), and for Tirana (the capital) county were respectively; 6,807 (42.8%) and 9,089 (57.2%).

Age on first admission mean (median) was 35.2 ± 21.2 (36.3) years. Tirana (the capital) county, age on first admission mean (median) was 35.1 ± 22.1 (36.0) years. Age on first admission, mean (median), for the two major categories ‘Mental Disorders’ and ‘Other’ were respectively; 36.9 ± 15.5 (36.3) years and 34.0 ± 25.2 (35.0) years, and for Tirana (the capital) county were respectively; 37.7 ± 15.4 (37.2) years and 33.0 ± 26.3 (31.0) years. Comparative analysis shows significant difference between age on first admission between major classification ‘Mental Disorders’ and ‘Other’, Tirana county, F (172.0), $p < 0.001$, eta-squared ($\eta p2$) =0.011.Age on first admission, mean (median), for the two major categories ‘Mental Disorders’ and ‘Other’ were respectively for Tirana (the capital) county were respectively; male (36.2 ± 15.4 (35.3) years and 32.4 ± 26.4 (28.0) years, $p<0.001$) and female (39.4 ± 15.4 (39.6) years and 33.8 ± 33.0 (26.0) years, $p<0.019$). For all mental disorders sex

age differences were significant, p<0.001and for the category 'other' sex age differences were not significant p=0.402.

Age on first admission, mean (median), for some diagnoses for Tirana (the capital) county were respectively; Malignant neoplasm of brain 49.5 ± 19.5 (53.0) years, Schizophrenic disorders 38.1 ± 11.4 (37.0) years, Parkinson's disease 61.6 ± 10.2 (61.0) years, Multiple sclerosis 37.6 ± 12.3 (37.0) years and Epilepsy and recurrent seizures 20.3 ± 23.0 (10.0) years. Comparative analysis shows significant difference between age on first admission between '295-Schizophrenic disorders' and 'Primary Malignant Neoplasm of Brain (PMNB)', Tirana county, F (351.0), $p < 0.001$, eta-squared (ηp^2) =0.119.

DISCUSSION

World Health Organization (WHO) accepts the concept of social determinants of health of which income inequality and socioeconomic disadvantage are approved. Physiologically the dentate gyrus of hippocampus exhibits self-renewal and multipotency showing through a rodent brain model the possibility of neural stem cells to initiate gliomagenesis.[23] The same brain region shows deviations in both, early and late schizophrenia stages. Further, animal models involved environmental factors to hippocampus abnormal activity.[7] Actually there is not controversy on accepting multifaceted models of risk factors for malignant brain tumors or schizophrenia and the overlapping is possible which requires quantification as a causative or at least risk factor. The questions, 'Does the brain respond the same way to risk factors at different ages?' and 'Are there common epigenetic or molecular promoting mechanisms for Primary Malignant Neoplasm of Brain (PMNB) and Serious Mental Illness (SMI)?'

External triggers of psychosis as Cannabis does with a 41% risk increase from users and urbanization and higher economic status association with increased occurrence of malignant brain tumors can start the discussion.[23-24] Brain is very selective about biological material input. The best example is the blood brain barrier (BBB) and long half-life, 5 years, of brain cholesterol which in itself cannot cross BBB, making it completely separated from cholesterol in blood.[25] While, when it comes to sensorial inputs the brain works to gather most of it. Many factors as neuroplasticity, neuron replacement, number of neurons to total brain cells (10%) and the example emotional tainting of memories from neurons transiting from amygdala to the hippocampus require a holistic approach and framework.[25] Organoids generating from schizophrenia patients show neurodevelopmental aberrations, one of which is neuronal differentiation, suggesting predisposition to encounter the condition.[26] These facts support a framework of different age expression of the two entities in discussion. Schizophrenia age of onset show a pattern of more incident male cases in adolescence and a reversal of trend higher in females from the age of 40.[27] The major number primary glioblastomas occur the sixth decade of life and later. Our data show a mean (median) age for 'Malignant neoplasms of brain', 49.5 ± 19.5 (53.0) years.[23] Non consistent findings support the idea that persons with schizophrenia show lower incidence of glioma. Research on molecular defects and microRNA changes related to schizophrenia are possible protective actors against glioma.[28] At this point the age of onset distribution as suggested (Figure.1) would be the expression of externalization of brain response to common risk factors

but different diagnostic entities because brain maturation and aging. The normality of the new age distribution is scrutinized, a point of intersection from two distributions is represented. Using the age of first admission as a surrogate representation of the age of onset is one of the main study limitations. Financial problems and unemployment are ongoing stressors for psychosis.[29] Psychological trauma increases systemic inflammation markers or is promoted by them and inflammation is supposed as a promoter of tumor development. High levels of inflammation supposedly can be a common promoter of mental disorders and tumor development, which doesn't explain the qualitative brain age differences which make two different diagnoses, psychosis vs cancer, as the effect (partially) of their common starter, inflammation.[23]

Although the normal distributions approximations are a common fact in medicine all our original age distributions of grouped diseases didn't pass the normality test, all ages or age >15 years (Table 2) Kolmogorov-Smirnov ($p<0.001$).[30] Age-specific transformation of the age-groups, except 'Hereditary and degenerative diseases of the central nervous system' (330-337), $p=0.011$, data tested positively towards a normal distribution (Table 3). Age-specific transformation are rates (number of age-groups

Table 1. Number of first admission, capital (Tirana), by code-blocks, 'Epilepsy and recurrent seizures' excluded, 2005-21. (Appendix A)

Age-group	Mental Disorders	Other	Total	(140-239)	(290-299)	(300-319)	(330-337)	(340-349)
<1 year	0 (0.0%)	12 (0.3%)	12 (0.%1)	5(0.3)	0(0)	0(0)	1(0.1)	6(0.4)
1-4 years	108 (1.6%)	131 (3.3%)	239 (2.2%)	33(1.9)	66(1.2)	42(2.8)	3(0.4)	95(6.5)
5-9 years	173 (2.5%)	104 (2.6%)	277 (2.6%)	37(2.1)	90(1.7)	83(5.4)	1(0.1)	66(4.5)
10-14 years	138 (2.0%)	127 (3.2%)	265 (2.5%)	40(2.3)	44(0.8)	94(6.2)	0(0)	87(6)
15-19 years	371 (5.5%)	88 (2.2%)	459 (4.3%)	31(1.8)	173(3.3)	198(13)	3(0.4)	54(3.7)
20-24 years	689 (10.1%)	134 (3.4%)	823 (7.6%)	52(3)	535(10.1)	154(10.1)	3(0.4)	79(5.4)
25-29 years	747 (11.0%)	166 (4.2%)	913 (8.5%)	62(3.6)	613(11.6)	134(8.8)	7(0.9)	97(6.7)
30-34 years	785 (11.5%)	169 (4.3%)	954 (8.9%)	58(3.3)	654(12.4)	131(8.6)	4(0.5)	107(7.4)
35-39 years	795 (11.7%)	186 (4.7%)	981 (9.1%)	80(4.6)	641(12.1)	154(10.1)	7(0.9)	99(6.8)
40-44 years	731 (10.7%)	245 (6.2%)	976 (9.1%)	116(6.7)	596(11.3)	135(8.9)	21(2.7)	108(7.4)
45-49 years	777 (11.4%)	332 (8.4%)	1109 (10.3%)	171(9.8)	646(12.2)	131(8.6)	45(5.8)	116(8)
50-54 years	548 (8.1%)	411 (10.4%)	959 (8.9%)	194(11.2)	448(8.5)	100(6.6)	87(11.2)	130(8.9)
55-59 years	410 (6.0%)	484 (12.2%)	894 (8.3%)	235(13.5)	344(6.5)	66(4.3)	150(19.3)	99(6.8)
60-64 years	234 (3.4%)	489 (12.3%)	723 (6.7%)	240(13.8)	192(3.6)	42(2.8)	149(19.1)	100(6.9)
65-69 years	166 (2.4%)	367 (9.2%)	533 (4.9%)	199(11.5)	129(2.4)	37(2.4)	99(12.7)	69(4.7)
70-74 years	75 (1.1%)	231 (5.8%)	306(2.8%)	101(5.8)	61(1.2)	14(0.9)	80(10.3)	50(3.4)
75-79 years	47 (0.7%)	156 (3.9%)	203 (1.9%)	56(3.2)	39(0.7)	8(0.5)	63(8.1)	37(2.5)
80-84 years	11 (0.2%)	91 (2.3%)	102 (0.9%)	21(1.2)	11(0.2)	0(0)	38(4.9)	32(2.2)
85+ years	2 (0.0%)	47 (1.2%)	49 (0.5%)	6(0.3)	2(0)	0(0)	18(2.3)	23(1.6)
Total	6807 (100%)	3970 (100%)	10777 (100%)	1737(100)	5284(100)	1523(100)	779(100)	1454(100)
Mean ± SD	37.7 ± 15.5	48.9 ± 20.5	41.8 ± 18.3	50.5 ± 18.4	39.1 ± 14.7	32.9 ± 16.9	61.6 ± 12.8	40.2 ± 22.3
Median	37.2	53	42.2	54.3	38.3	32.1	61	41
Sig.*	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

*Sig. - Kolmogorov-Smirnov

Table 2. Age-specific, number of first admission, capital (Tirana), by code-blocks, 'Epilepsy and recurrent seizures' excluded. (Appendix A)

Age-group	Mental Disorders	Other	Total	(140-239)	(290-299)	(300-319)	(330-337)	(340-349)
0-4 years	15.2 (43.0%)	20.1 (57.0%)	35.3 (100%)	5.3 (15.1%)	9.3 (26.3%)	5.9 (16.7%)	0.6 (1.6%)	14.2 (40.2%)
5-9 years	21.4 (62.5%)	12.8 (37.5%)	34.2 (100%)	4.6 (13.4%)	11.1 (32.5%)	10.2 (30.0%)	0.1 (0.4%)	8.1 (23.8%)
10-14 years	15.6 (52.1%)	14.4 (47.9%)	30.0 (100%)	4.5 (15.1%)	5.0 (16.6%)	10.6 (35.5%)	0.0 (0.0%)	9.9 (32.8%)
15-19 years	36.6 (80.8%)	8.7 (19.2%)	45.3 (100%)	3.1 (6.8%)	17.1 (37.7%)	19.5 (43.1%)	0.3 (0.7%)	5.3 (11.8%)
20-24 years	65.2 (83.7%)	12.7 (16.3%)	77.9 (100%)	4.9 (6.3%)	50.6 (65.0%)	14.6 (18.7%)	0.3 (0.4%)	7.5 (9.6%)
25-29 years	79.6 (81.8%)	17.7 (18.2%)	97.3 (100%)	6.6 (6.8%)	65.3 (67.1%)	14.3 (14.7%)	0.7 (0.8%)	10.3 (10.6%)
30-34 years	92.5 (82.3%)	19.9 (17.7%)	112.5 (100%)	6.8 (6.1%)	77.1 (68.6%)	15.4 (13.7%)	0.5 (0.4%)	12.6 (11.2%)
35-39 years	94.7 (81.0%)	22.1 (19.0%)	116.8 (100%)	9.5 (8.2%)	76.3 (65.3%)	18.3 (15.7%)	0.8 (0.7%)	11.8 (10.1%)
40-44 years	87.7 (74.9%)	29.4 (25.1%)	117.2 (100%)	13.9 (11.9%)	71.5 (61.1%)	16.2 (13.8%)	2.5 (2.2%)	13.0 (11.1%)
45-49 years	92.1 (70.1%)	39.3 (29.9%)	131.4 (100%)	20.3 (15.4%)	76.5 (58.3%)	15.5 (11.8%)	5.3 (4.1%)	13.7 (10.5%)
50-54 years	63.3 (57.1%)	47.5 (42.9%)	110.8 (100%)	22.4 (20.2%)	51.8 (46.7%)	11.6 (10.4%)	10.1 (9.1%)	15.0 (13.6%)
55-59 years	52.2 (45.9%)	61.6 (54.1%)	113.8 (100%)	29.9 (26.3%)	43.8 (38.5%)	8.4 (7.4%)	19.1 (16.8%)	12.6 (11.1%)
60-64 years	32.2 (32.4%)	67.4 (67.6%)	99.6 (100%)	33.1 (33.2%)	26.5 (26.6%)	5.8 (5.8%)	20.5 (20.6%)	13.8 (13.8%)
65-69 years	26.9 (31.1%)	59.5 (68.9%)	86.3 (100%)	32.2 (37.3%)	20.9 (24.2%)	6.0 (6.9%)	16.0 (18.6%)	11.2 (12.9%)
70-74 years	15.1 (24.5%)	46.6 (75.5%)	61.7 (100%)	20.4 (33.0%)	12.3 (19.9%)	2.8 (4.6%)	16.1 (26.1%)	10.1 (16.3%)
75-79 years	14.6 (23.2%)	48.4 (76.8%)	63.0 (100%)	17.4 (27.6%)	12.1 (19.2%)	2.5 (3.9%)	19.5 (31.0%)	11.5 (18.2%)
80-84 years	5.1 (10.8%)	42.3 (89.2%)	47.5 (100%)	9.8 (20.6%)	5.1 (10.8%)	0.0 (0.0%)	17.7 (37.3%)	14.9 (31.4%)
85+ years	1.5 (4.1%)	35.4 (95.9%)	36.9 (100%)	4.5 (12.2%)	1.5 (4.1%)	0.0 (0.0%)	13.5 (36.7%)	17.3 (46.9%)
Total	52.6 (63.2%)	30.7 (36.8%)	83.3 (100%)	13.4 (16.1%)	40.8 (49.0%)	11.8(14.1%)	6.0 (7.2%)	11.2 (13.5%)
Skewness (SE)	-0.033 (0.580)	0.024 (0.580)	-0.378 (0.580)	0.499 (0.580)	0.054 (0.580)	-0.233 (0.580)	0.128 (0.040)	-0.633 (0.580)
Kurtosis (SE)	-1.594 (1.121)	-1.104 (1. 121)	-1.149 (1. 121)	-1.284 (1. 121)	-1.706 (1. 121)	-1.503 (1. 121)	-1.944 (1. 121)	0.905 (1. 121)
Sig.	0.124	0.682	0.197	0.114	0.065	0.140	0.011	0.771

*Sig. - Shapiro-Wilk. The statistical test was performed for age-groups 15-19 years and higher.
** Age-groups were constructed second INSTAT, Albania aggregated data age-groups.

= 15) requiring the z value to fall in the range of ± 1.96 to establish data normality.[31] Z (Z = Skew value / SE skewness) value (the critical ratio), skewness and kurtosis show evidence of normally distributed values (Table 3). A last calculation was the "95% range check."[32] When we perform the "95% range check", the age-group (age >15 years) data for 'mental disorders' don't pass the test, taking negative values for -2SD, while 'Other' and 'Total' pass the test. Considering that 'Total' is the variable of interest we don't need to logarithmically transform the data. These results have to be confronted in addition with the theorem for normally distributed variables which states that; any linear combination of independent normally distributed random variables xi (i = 1, 2, . . ., n) is also distributed according to the normal distribution.[33] Our data conform to the theorem for Shapiro-Wilk test, skewness, kurtosis, and Z value (the critical ratio). Only 'mental disorders' doesn't pass the "95% range check". 'Other' and 'Total' pass the "95% range check". If "95% range check" for

Table 3. All involved diagnoses, 2005-21, ICD-9 three-digit code. (Appendix A)

	Capital (Tirana)	First (NO)		ICD-9 code - Diagnosis	First (YES)		Total
		NO (%)	YES (%)		YES (%)	NO (%)	
Mental Disorders	Psychoses (290-299)	3 (0.0)	10 (0.1)	290-Dementias	33 (0.2)	23 (0.1)	69 (0.1)
		874 (13.8)	3085 (29.7)	295-Schizophrenic disorders	1760 (11.1)	1153 (7.4)	6872 (14.2)
		1056 (16.7)	2049 (19.7)	296-Episodic mood disorders	2543 (16.0)	2029 (12.9)	7677 (15.9)
		45 (0.7)	160 (1.5)	297-Delusional disorders	195 (1.2)	93 (0.6)	493 (1.0)
		106 (1.7)	205 (2.0)	298-Other nonorganic psychoses	520 (3.3)	366 (2.3)	1197 (2.5)
		33 (0.5)	97 (0.9)	299-Pervasive developmental disorders	233 (1.5)	98 (0.6)	461 (1.0)
	Other mental disorders (300-319)	84 (1.3)	144 (1.4)	300-Anxiety, dissociative and somatoform disorders	394 (2.5)	358 (2.3)	980 (2.0)
		51 (0.8)	361 (3.5)	301-Personality disorders	307 (1.9)	165 (1.1)	884 (1.8)
		2 (0.0)	15 (0.1)	302-Sexual and gender identity disorders	11 (0.1)	3 (0.0)	31 (0.1)
		0 (0.0)	4 (0.0)	306-Physiological malfunction arising from mental factors	10 (0.1)	21 (0.1)	35 (0.1)
		5 (0.1)	7 (0.1)	307-Special symptoms or syndromes, not elsewhere classified	27 (0.2)	18 (0.1)	57 (0.1)
		3 (0.0)	6 (0.1)	308-Acute reaction to stress	20 (0.1)	11 (0.1)	40 (0.1)
		25 (0.4)	45 (0.4)	309-Adjustment reaction	181 (1.1)	138 (0.9)	389 (0.8)
		4 (0.1)	14 (0.1)	310-Specific nonpsychotic mental disorders due to brain damage	18 (0.1)	14 (0.1)	50 (0.1)
		15 (0.2)	36 (0.3)	311-Depressive disorder, not elsewhere classified	64 (0.4)	50 (3.0)	165 (0.3)
		26 (0.4)	52 (0.5)	312-Disturbance of conduct, not elsewhere classified	90 (0.6)	87 (0.6)	255 (0.5)
		16 (0.3)	14 (0.1)	313-Disturbance of emotions specific to childhood and adolescence	43 (0.3)	32 (0.2)	105 (0.2)
		1 (0.0)	1 (0.0)	314-Hyperkinetic syndrome of childhood	5 (0.0)	6 (0.0)	13 (0.0)
		7 (0.1)	27 (0.3)	315-Specific delays in development	11 (0.1)	38 (0.2)	83 (0.2)
		2 (0.0)	8 (0.1)	316-Psychic factors associated with diseases classified elsewhere	5 (0.0)	4 (0.0)	19 (0.0)
		13 (0.2)	41 (0.4)	317-Mild intellectual disabilities	137 (0.9)	114 (0.7)	305 (0.6)
		16 (0.3)	48 (0.5)	318-Other specified intellectual disabilities	189 (1.2)	96 (0.6)	349 (0.7)
		0 (0.0)	1 (0.0)	319-Profound intellectual disabilities	11 (0.1)	7 (0.0)	19 (0.0)
Other	Neoplasms (140-239)	848 (13.4)	503 (4.8)	191-Malignant neoplasm of brain	849 (5.3)	1815 (11.6)	4015 (8.3)
		434 (6.9)	230 (2.2)	225-Benign neoplasm of brain and other parts of nervous system	888 (5.6)	1778 (11.3)	3330 (6.9)
	(330-337) *	46 (0.7)	50 (0.5)	331-Other cerebral degenerations	258 (1.6)	197 (1.3)	551 (1.1)
		219 (3.5)	285 (2.7)	332-Parkinson's disease	521 (3.3)	539 (3.4)	1564 (3.2)
	Other disorders of the central nervous system (340-349)	443 (7.0)	460 (4.4)	340-Multiple sclerosis	450 (2.8)	577 (3.7)	1930 (4.0)
		25 (0.4)	29 (0.3)	341-Other demyelinating diseases of central nervous system	128 (0.8)	153 (1.0)	335 (0.7)
		145 (2.3)	165 (1.6)	344-Other paralytic syndromes	876 (5.5)	999 (6.4)	2185 (4.5)
		1185 (18.8)	1722 (16.6)	345-Epilepsy and recurrent seizures	4522 (28.5)	3821 (24.4)	11250 (23.3)
		586 (9.3)	508 (4.9)	348-Other conditions of brain	597 (3.8)	904 (5.8)	2595 (5.4)
	Total	6318 (100.0)	10382 (100.0)	Total	15896 (100.0)	15707 (100.0)	48303 (100.0)

*Hereditary and degenerative diseases of the central nervous system (330-337)

'mental disorders' (Table 1 classification) but not for other normality tests break the validity of the theorem in our data or not requires cumulative evidence from similar studies. (Figure 3) and (Figure 4) visually show similarities to the normal distribution patterns.

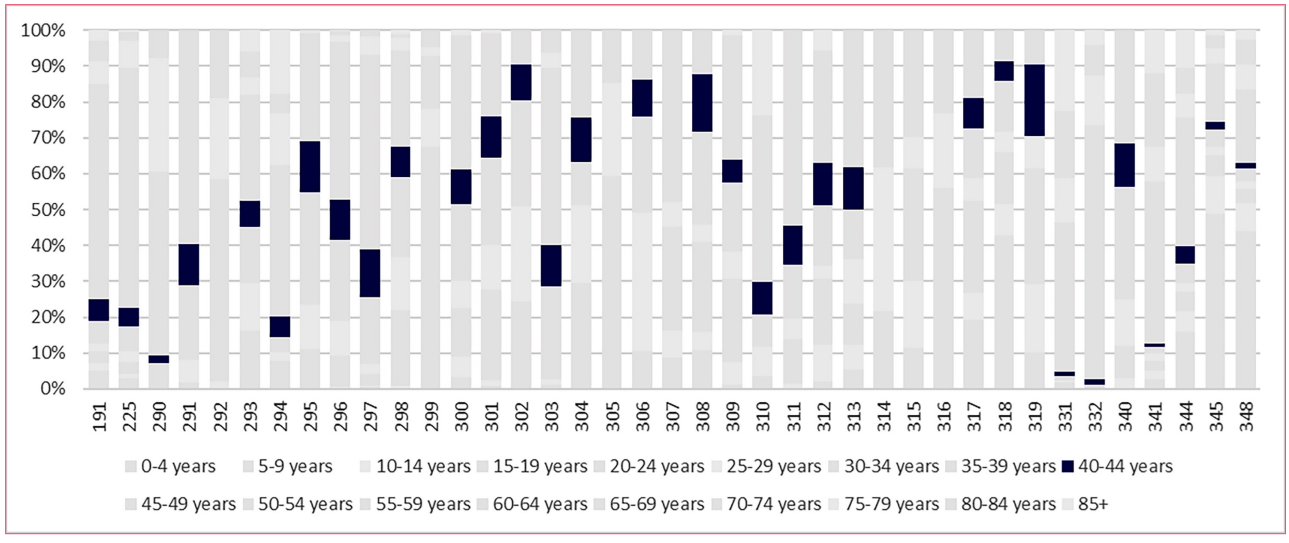

Figure 2. First admissions frequency (Tirana), by code-blocks and type of grouped disorders, 15 years and older.
The age-specific distribution 15 years and older serves as a minimal standardization method to project hospital data on the whole population. Age-specific crude rates were calculated referring to INSTAT Albania censuses 2011 and 2023

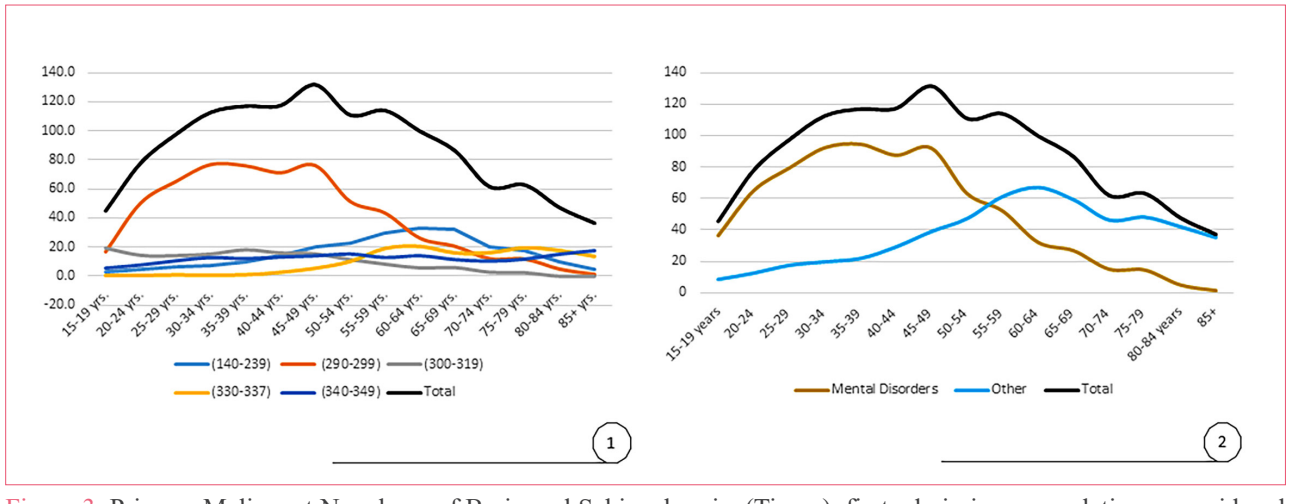

Figure 3. Primary Malignant Neoplasm of Brain and Schizophrenia, (Tirana), first admissions, population pyramid and cumulative age distribution, 15 years and older.
The two central diagnoses for each group 'Mental Disorders'- Schizophrenia and 'Other'- Primary Malignant Neoplasm of Brain were selected for further comparison. Age-specific crude rates were calculated referring to INSTAT Albania censuses 2011 and 2023

A theoretical parallel can be made with Jung (Jung, 2014) when he distinguishes a cutoff, the middle age, with different goals; before it, working on socio-economic status and procreation, followed after middle age on neglected and non-evolved aspects of his/her personality.[34] A development of this perspective can suggest that the human brain is setup with priority and secondary goals, overturned

after a certain age. What was a priority become a secondary goal because of realization and security, paving the way for the new shadowy goals. Disruption or inflation of the nonpriority goal brings unusual pressure resulting in a non-physiological, contrary to physiological response toward inflation of the primary goal. For example, a young person would be much more elastic towards socio-economic status catastrophes than a sixty-year-old one. This reasoning seems to go along with our hypothesis of different diagnosis expression in relation to the same cutoff. Indeed, the importance of this social structure in the creation and dissemination of a reputation means that reputation is not an asset that you own. Instead it is created within the set of beliefs, perceptions and evaluations a community forms about you. Indeed, the importance of this social structure in the creation and dissemination of a reputation means that reputation is not an asset that you own. Instead it is created within the set of beliefs, perceptions and evaluations a community forms about you.[35]

A simple similar method of translational research can be the example of the use of SARS-CoV-2 rapid diagnostic tests is technically beneficial based on IgM and IgG peaking values. IgM antibody levels peak early while levels of IgG antibody persist up to 90 days after symptom onset, while IgM usually decline after one month if infection.[36-37] Decision making is based on concomitant analysis of both immunoglobulins' curves. Diagnosis classified as brain diagnoses, have a colorful age distribution. The 40-44 years' age-group emphasis (Figure 2) is a good visual representation.

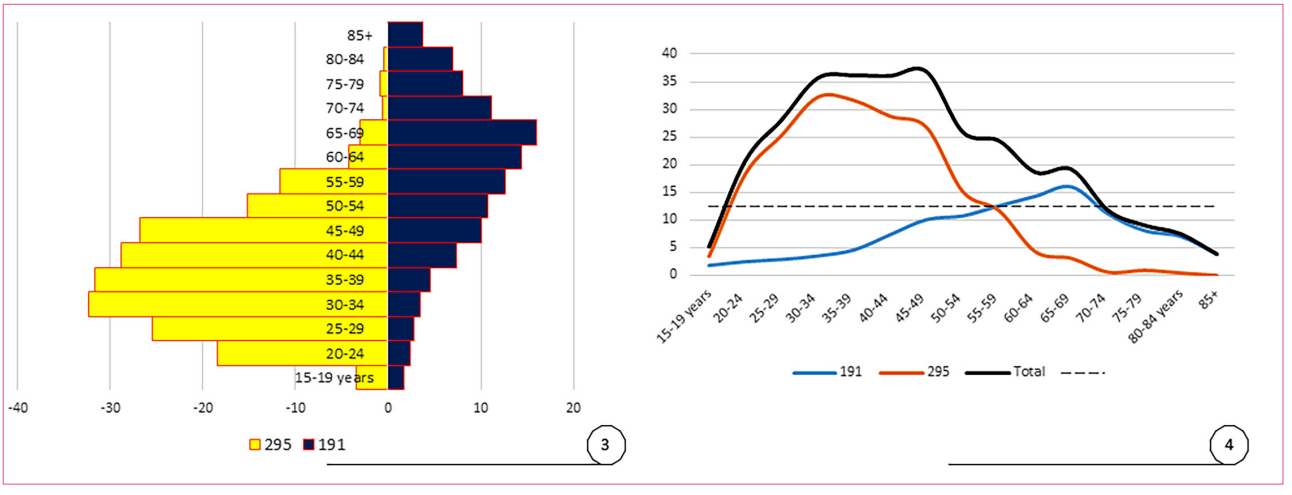

Figure 4. Stacked column chart, all involved diagnoses, age specific, 2005-21, ICD-9 three-digit code.
The 40-44 years' age-group is the middle group on our age-groups categorization. It was highlighted to show the distribution of diagnoses frequency (first admissions as the surrogate of age of onset) by age group compared to each other.

The continuity of the two groups of diagnoses as the cohort ages combined with the normal distribution approximation doesn't prove common causative factors. Neither the results find a relative cut-off the brain cells change qualitatively. The results open the door to this kind of arguments. The question is; do primary brain tumors and psychiatric disease are the expression of the same group of conditions acting in a changing subject, the maturing and aging brain, or the brain facing different kind of pressure, age dependent, responds with different pathologies, or both. Both means that the aging brain matures, which means choses different challenges, as the subject and object of

conscience, being a victim of itself and environmental pressure when can't outfight the problem (s). An example can be the economic challenges people have to face with aging. The responsibilities of a teenager, a young adult, a working man and elderly people clearly differ. At this point, as the age is crucial, the study of financial health burden as a push to schizophrenia can be scrutinized comparing median age of male and female subjects to their financial pressure. Technically speaking, do age correlates with financial pressure, do financial burden and shape is similar for men and women in different age groups when schizophrenia peaks!

Recommendations holds the idea that epidemiological research must be performed on comparing epigenetic factors, among others, originally supporting the idea that the negative correlation of these diagnoses (Glioma in Schizophrenia) expression is not casual.[28] In case we accept brain lateralization functions a hypothesis correlating brain tumor side of the brain expression to previous, for example a hypothesis of financial trauma, would be of study interest.[38] Especially in the ground of the rarity pediatric tumors occur in adults and adult tumors which rarely appear in children opens to further investigation from our study prospect.[39]

CONCLUSION

Grouping primary brain diseases and mental disorders on grounds of brain tissue involved in the pathological processes makes sense developmentally, anatomically, pathophysiologically and semiologically. A hypothesis accusing complex socio-economic environmental agents as contributing risk factors to a disease would require its application to a mature population. On this conditions the approximation to normal distribution of age on first hospitalization of this grouping doesn't prove a continuum of such diverse diagnoses happen because the same factor (s) act at least dicotomically on an aging brain which, first responds with mental health issues and later with cellular damage like brain malignant tumors, but entices further investigation suggesting that the findings about age distribution mirror individuals' brain response to continuous challenges it is exposed.

Conflict of Interests

The author declares that he has no conflicts of interest.

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