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Brain abnormalities on neuroimaging in Children with Congenital Zika Syndrome in Salvador, Brazil and its possible implications on neuropsychological development

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Conflict of interest disclosure

We declare that no author has a conflict of interest.

Ethics approval statement

The research project, which integrates this study, was approved by the Ethics Committee of the Institute of Collective Health of the Federal University of Bahia, under the number 1.659.107.

Data Availability Statement

Author elects to not share data.

ABSTRACT

Objective: to characterize the spectrum of brain damages presented in children affected by Congenital Zika Syndrome (CZS), verify the existence of a co-occurrence pattern of these damages and discuss possible implications for the neuropsychological development. Methods: descriptive, quantitative, individualized and cross-sectional study using secondary sources. We selected 136 children with CZS from the database of the Center of Strategic Information on Health Vigilance of the Municipal Office of Salvador, Brazil. We conducted descriptive and multiple correspondence analyses. Results: Among the set of analyzed variables, microcephaly (51.5%), ventriculomegaly (57.4%) and brain calcifications (77.2%) were identified as the most frequent. The multiple correspondence analysis showed that the combination of these three variables (32.4%) was what better represented the spectrum of brain damages in the Central Nervous System. Interpretation: Damage in the sensory-motor, cognitive and language development, as well as neurodevelopmental disorders, are described in the literature as impairments associated, either isolated or combined, with these damages, and it is worth highlighting that, in combined brain damages, impairments tend to be more severe. The findings of this study may contribute to understanding the repercussions of CZS on the neuropsychological development of children affected by the epidemic.

Keywords: Congenital Zika Syndrome; neurological spectrum; neuropsychological development.

1. INTRODUCTION

Phylogenetic studies indicate that the Zika virus (ZIKV) was probably introduced in Brazil in 2013[1], but only in April 2015 it was first identified in the country, being recognized as the causative agent of a rash-disease outbreak in Brazil's Northeast region[2,3]. Only in Salvador, the country's fourth largest city and one of the epicenters of the ZIKV epidemic in the Northeast, almost 15,000 cases of a rash disease attributed to ZIKV were reported between February and June 2015[4].

Initially, ZIKV infections were considered of little relevance due to their self-limited and poorly symptomatic clinical picture. However, in the months following the peak of the ZIKV epidemic, there was an increase in records of children born with microcephaly, which was later associated[5] with ZIKV infection during pregnancy[6]. Until the end of 2015, more than 3,000 babies with microcephaly, corresponding to 20 cases for every 10,000 births, were recorded in Brazil[6]. Later, it was observed that, besides microcephaly, children affected by an intrauterine ZIKV infection had a series of brain damages, as well as damages in other organs and systems, which led to the recognition of the Congenital Zika Syndrome (CZS)[7].

CZS is characterized by serious and direct brain damages in brain volume, including structural and functional components observed through neuroimaging examinations of the Central Nervous System (CNS), such as transfontanellar ultrasound, computed tomography and magnetic resonance[8]. Are characteristics of the CZS: severe microcephaly with partially collapsed skull; thin cerebral cortices with subcortical calcifications; ocular changes, such as macular scarring and pigments in the center of the retina; arthrogryposis; as well as congenital contractures, early hypertonia and symptoms of extrapyramidal involvement, among others[8,9].

Although evidence suggests that ZIKV infections can occur during any gestation stage, associations with brain damages in the embryo or fetus are more frequent during the first trimester[10]and, when the infection occurs during this time, there is an increased chance of abortion, stillbirth, early mortality and microcephaly[9]. Although it has been shown that the brain damages seen in this syndrome are associated with neurodevelopmental impairments, such as language and cognition deficits and problems in motor and behavioral skills[11,12], the literature on the subject is still scarce, hindering the understanding of the occurrence patterns of the brain damages and the possible consequences for the neurodevelopment of children.

This study aimed to characterize the spectrum of brain damages detected by neuroimaging examination of children with confirmed CZS in Salvador, Bahia, Brazil, verify the existence of a co-occurrence pattern of these damages and discuss the possible implications for the neuropsychological development of this generation.

2. METHODS

2.1 Study design

This is a descriptive, quantitative, individualized and cross-sectional study.

2.2 Sample selection

We selected the sample of this study from the database containing the case records of microcephaly and CZS provided by the Center of Strategic Information on Health Vigilance (Centro de Informações Estratégicas de Vigilância em Saúde, CIEVS) from Salvador's municipal office. This database was previously used to characterize CZS cases in Salvador and evaluate the accuracy of measuring the cephalic perimeter to detect children with CZS[13]. During the use of the database in December 2016, there were 714 reports of children born in Salvador between 01/08/2015 and 31/07/2016. This period corresponds to that with the largest number of children born with suspected CZS[14]. Among the reported cases, 433 (60.6%) had their investigation concluded by Center of Strategic Information on Health Vigilance, of which 47.1% (204/433) were confirmed. In November 2017, based on new investigations, 22 confirmed cases born in this period were included, totaling a sample of 224 children. Of these, 136 (60.7%) were selected with complete information on the relevant variables for this study. Of the remain, 38 (43,2%) were positive for STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex) and 50 (56,8%) were missing data for variables of interest. In addition there was no difference between those who were selected or excluded. The mean for maternal age was 26,7 years (SD 6,35) for participants and 27,4 (SD 7,9) for the loss; gestacional age correspond to 37 weeks (SD 3,2) and 36 (SD 4,1) respectively; and 58% of girls participating, against 63% not involved.

2.3 Criteria for reporting CZS cases

The criteria used to report and confirm the cases included in this study followed protocols established by the Ministry of Health, which changed in the course of the CZS epidemic[15, 16, 7].

2.4 Criteria for excluding cases

We excluded, from this study, children that had positive laboratory results for any of the STORCH or had genetic alterations.

2.5 Definition of the variables

The analyzed variables were: 1) Age of the mother; 2) Self-declared race; 3) Income of the mother; 4) Marital status of the mother; 5) Education level of the mother; 5) Number of children in the same gestation; 6) Prenatal care; 7) Number of prenatal visits; 8) Drinking and smoking habits during gestation; 9) Rash during gestation; 10) Pruritus during gestation; 11) Fever during gestation; 12) Trimester in which rash occurred; 13) Sex of the baby; 14) Type of delivery; 15) Weight at birth; 16) Apgar at 1 and 5 minutes after birth; 17) Time of detection of brain damages; 18) Occurrence of microcephaly according to the Intergrowth-21st table; 19) Calcifications; 20) Ventriculomegaly; 21) Subependymal cysts; 22) Dysgenesis of the corpus callosum; 23) Agenesis of the corpus callosum; 24) Hydrocephalus; 25) Lissencephaly.

2.6 Analysis Plan

To tabulate and organize the database, we used the software SPSS v. 25 *IBM Corporation*. For the descriptive analyses, we calculated absolute and relative frequencies. Aiming to identify co-occurrence patterns of some brain damages, we used a multiple correspondence analysis by means of the software R *Foundation for Statistical Computing,* the packages used were *FactoMineR* and *factoextra*. This analysis was conducted to explore the reduction of categorical variables, determining the degree of global association between observations and variables, and allowing to perceive possible associations between variables regarding some brain damages seen in the children's neuroimaging examinations[17, 18]. The generated graphs are formed by crossing the two dimensions that better explain the data variability, each dimension consisting of the variables with the highest values of relative contribution. The graphs show the position of each response category so that these positions can be interpreted as associations between response patterns. Dots that appear together in the graph suggest a stronger association between the brain damages categories, forming groups that are displayed using oval diagrams[17].

2.7 Ethical considerations

The research project “Effects of the congenital neurological manifestations associated with Zika virus on children development: a prospective cohort study in the primary care context in Salvador-BA”, which integrates this study, was approved by the Ethics Committee of the Institute of Collective Health of the Federal University of Bahia, under the number 1.659.107, meeting the

requirements of the Resolution 466/12 of the National Health Council regarding research with human beings.

The children that took part in this study were inserted in a longitudinal prospective research study to follow child development with measurements of cognitive, language and motor development evaluated through the Bayley-III Scale. They comprise the cohort DICa, in follow up at the Institute of Collective Health of the Federal University of Bahia.

2.8 Literature Review

To discuss the probable implications of CZS for the neuropsychological development, we conducted an unsystematic literature review, through the snow-ball method using the Database of the CAPES Portal of articles published in the last 20 years. We used the following descriptors: "microcephaly and neurodevelopment"; "ventriculomegaly and neurodevelopment"; "calcifications and neurodevelopment".

3. RESULTS

Among the 136 analyzed children, the median of the age of the mothers was 27 (15–44) years. Most mothers (116/136, 85.3%) were between 16 and 34 years old and 91.3% (115/126) declared themselves as black. Regarding family income, 60.6% (40/66) lived with less than one minimum wage per month. Regarding marital status, 54.2% were single, with 53.2% having concluded high school. Only 12.6% (14/111) had a college degree.

On gestation history, 94.7% (126/133) generated a single child, 98.4% (124/126) had prenatal care, with 71.1% (86/121) having more than 6 visits. A total of 12.1% (16/132) consumed alcohol or tobacco during the gestation. There were reports of symptoms suggesting ZIKV infection, such as rash (79/121, 65.3%), fever (45/115, 39.1%) and pruritus (61/121, 50.4%). Rash appeared mostly in the first gestational trimester (53/81, 65.4%).

Regarding the babies, 79 (79/136) were female, 28.6% (38/133) were premature and 36.3% (49/135) had low weight at birth (< 2500g). Most had an adequate performance on Apgar (8-10), with 81.1% (107/132) one minute and 96.2% (127/132) five minutes after birth.

Of the children confirmed for CZS, 64% had brain damages detected in the postpartum period (87/101, 64%). The cephalic perimeter of 48.5% of the children was within the normal range,

19.1% were diagnosed with microcephaly and 32.4% with severe microcephaly. Other brain damages are described in table 1.

Sixty-eight children had between three and five of the brain damages in the CNS included in this study. The others had fewer than three damages. The multiple correspondence analysis was initially performed with six variables regarding the brain damages that were present in more than 10% of the 136 children (ventriculomegaly, hydrocephalus, calcifications, subependymal cysts, microcephaly and dysgenesis of the corpus callosum). Based on the results, the variables hydrocephalus and subependymal cysts were excluded after the first level of analysis, indicating a relative contribution to inertia (variability) well below the usually recommended limit (1/Q, in which Q is the number of variables)[18]. The examination of the remaining variables allowed to identify the contribution of ventriculomegaly, calcifications and microcephaly for dimension 1, suggesting a co-occurrence pattern (Table 2). Dimension 2, consisting only of dysgenesis, explained only 25.3% of the data variability and was used only for comparison, while dimension 1 explained 39.9% (Table 2 and Figure 1). The figure 1 shows the main brain damages in the children of this study. Based on the results provided by the correspondence analysis, 44 (44/136, 32.4%) participants had co-occurrence of the three variables. The figure 2 indicate a significant difference between the categories of all variables.

4. DISCUSSION

The brain damages identified among the participants of this study confirm previous studies regarding the similarity of the damages in children affected by CZS[8,9]. The multiple correspondence analysis identified a global association between microcephaly, ventriculomegaly and calcifications, indicating a probable pattern of co-occurrence of changes in CZS. Combined brain damages are frequent in congenital syndromes and increase the degree of neurodevelopmental impairments[19,20]. While more frequent impairments include cerebral palsy, epilepsy, intellectual disability, language impairments, difficulty swallowing and anomalies of the visual and auditory systems. Attention-deficit/hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) were highlighted among the neurodevelopmental disorders[9,21], but there were babies who developed normally despite the presence of these abnormalities[22,23]. Microcephaly was absent in almost half of the studied children. However, other brain damages are also frequent in CZS[8,14], even in the absence of microcephaly[24].

Microcephaly has a role in determining the spectrum of neuropsychological and brain damages, as it is known that the smaller the cephalic perimeter the more serious the clinical picture presented by the child. Regarding our finding of 51.5% in cephalic perimeter change, it is likely that these children have a more prominent neurological impairment when compared to those without microcephaly. A risk of 10.5% for the occurrence of intellectual disability is estimated when the cephalic perimeter is between 2 and 3 standard deviations below the expected mean, increasing to 51.2% with a perimeter between 3 and 4 standard deviations and reaching 100% for those with 4 standard deviations below the mean[11]. A study with 82 children with cerebral palsy, probably related to CZS, used the Bayley-III scale to evaluate cognitive performance and found an association between very low cognitive performance and birth and follow-up cephalic perimeter, as well as between the motor score and follow-up cephalic perimeter [25]. The neuropsychological impairments differ according to cause, affected brain area and extension. A cephalic perimeter smaller than two standard deviations below the mean can be found in about 2% of the population but most have a normal intellectual performance[23].

Regarding CVS, studies revealed the possibility of microcephaly occurring after the first months of life in children that were born with an adequate cephalic perimeter, indicating that the virus' replication may continue in newborns[24]. Cognitive impairments in the first year may be absent among individuals that acquired microcephaly after birth or showed no other congenital anomaly at birth; however, impairments may appear during childhood or school years, requiring special educational and emotional support[9,26].

Sensory disabilities, when occurring together with microcephaly, may make the development even more difficult, because they reduce the capacity to learn and develop with the environment to which one belongs. Studies have indicated that one-year-old babies may show a cognitive development equivalent to that of two- or three-month-old babies, the worst performance being that of language[11].

Ventriculomegaly occurred in 57.4% of the investigated children. This is one of the most frequent impairments in congenital syndromes, characterized by the dilation of the cerebral ventricles and, although isolated from other brain damages, can generate delays, especially on motor and cognitive development[27]. A meta-analysis was conducted with 108 children that presented isolated unilateral ventriculomegaly from congenital or genetic changes and seven were diagnosed with

neurodevelopmental delay. The neuropsychological impairments were associated with different degrees of ventriculomegaly (mild – 10 to 12 mm; moderate – 12.1 to 14.9 mm; severe – > or = 15 mm), as well as with morphological or chromosomal anomalies and with the male sex[27].

It has been shown that the milder the degree of ventriculomegaly, the higher the probability of reaching a typical neurodevelopment[19,28], especially with a normal karyotype[28] and if the ventriculomegaly is isolated from other brain damages[18,28]. The atrial size considered the threshold (between 10 and 11 mm)[19] was also considered a good prognosis for the development of children with ventriculomegaly. Brain calcifications together with ventricular anomalies and microcephaly are common in congenital infections. Our study found 77.2% of brain calcifications. An investigation with 22 children whose mothers had toxoplasmosis during the pregnancy identified 72.7% of isolated calcifications or combined with other brain damages, being 40.9% with isolated calcifications, 9% combined with ventricular dilations, 4.5% with mild increase of the ventricles and the subarachnoid cisterns, 4.5% with porencephalic cyst, 4.5% with hydrocephalus and 4.5% combined with hydranencephaly[29]. In CZS, neuroimaging examinations have detected predominantly calcifications of diffuse and punctiform nature, mainly in the cortical-subcortical junction of the frontal and parietal lobes[25], as well as areas such as the brainstem, basal nuclei, periventricular region and thalamus[30]. In a study conducted with four infants up to 4 months old with presumable congenital ZIKV infection, having calcifications in the cortical-subcortical junction and ventriculomegaly, all participants were observed to have hyperreflexia and hypertonia, atypical development and deficit in hand function. The authors discuss the correlation of the outcomes with the referred brain damages[31].

From the results of our study and the scientific evidence, it is supposed that the isolated brain damages or, especially, those that exist in a co-occurrence pattern consisting of ventriculomegaly, calcifications and microcephaly, are associated with a set of neurodevelopmental impairments in children with CZS.

The level of impairment of these injuries has already been indicated by some studies[11,12,25]. After following 24 children with an average age of 19.9 months and confirmed diagnosis for CZS in Pernambuco, Brazil, a study[11] verified that they presented a developmental level equivalent to 2.1-month-old children for language, 2.7-month-old for global motricity, 3.1-month-old for fine motricity and 3.4-month-old for psychosocial features, evaluated by the Denver-II test. The

children did not walk or speak, which is expected from their age. Another study[12] evaluated 8 children with CSZ in Rio Grande do Norte, Brazil through the Bayley-III scale and compared them with typical children, both with an average age of 20.5 months. The authors found a significant delay in cognitive development, as well as in the motor domain in comparison with typical children. A third study[25] found a very low performance in the cognitive, motor and language performances of children with cerebral palsy probably associated with CZS.

One of the limitations of this study is the loss of 40% of subjects in the case selection due to incomplete data for the variables of interest, as well as those confirmed for STORCH, since these infections were not the object of this study. However, no relevant differences for child sex, maternal age and gestacional age at birth were observed between those who were selected or excluded.

In addition, the case definition for CZS supported by neuroimaging has not been confirmed by ZIKV sorology, weakening the association between neurological findings and maternal ZIKV infection. However, there was no availability of adequate tests to detect the virus at the time. Although the use of secondary data offers limitations, to our knowledge this research is the first to discuss data from the epidemiological surveillance center during the outbreak on the perspective of child development.

5. CONCLUSIONS

This study contributes to the knowledge of CZS and its spectrum of most frequent brain damages, identifying a co-occurrence pattern among these damages and discussing the possible effects on the neuropsychological development of children. The existence of a combination of brain damages tends to promote more severe impairments than those found when they occur in isolation. Thus, in any dimension of child development, adequate care needs to be offered, especially in an early stage.

6. ACKNOWLEDGMENTS

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7. AUTHOR CONTRIBUTION STATEMENT

Paula Sanders Pereira Pinto and Darci Neves dos Santos: planning, substantial contributions for the research strategy, acquisition, analysis and interpretation of the data; writing and review of the manuscript; approval of the submitted and final versions.

Thalita Madeira de Almeida; Lucas Monteiro; Mirela Maisa da Silva Souza; George Anderson Alves dos Santos; Cristiane Wanderley Cardoso; Letícia Marques dos Santos: substantial contributions for the research strategy, acquisition, analysis and interpretation of the data; writing and review of the manuscript; approval of the submitted and final versions.

Guilherme Sousa Ribeiro: writing and critical review of the article; approval of the submitted and final versions.

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Figure 1: Correspondece map for a multiple correspondence analysis activies variables.

Correspondence map with the categories of Calcifications, Dysgenesis, Microcephaly and Ventriculomegaly. Variable categories with a similar profile are grouped together (absence=0 and presence=1).

Figure 2: Confidence elipses round the categories of activies variables.

Confidence ellipses (95%) for categories of Calficications, Dysgenesis, Microcephaly and Ventriculomegaly. The objective is to see whether the categories of a categorical variable are significantly different from each other. Categories without ellipses intersection are significantly different (absence=0 and presence=1).

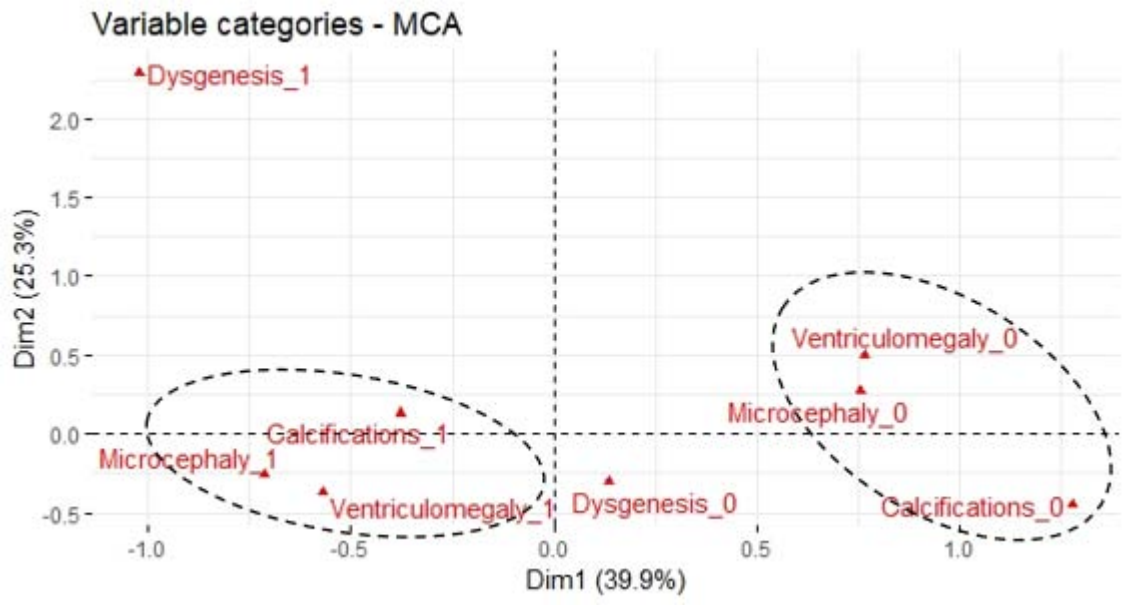
Table 1: Characteristics of the brain damages of children with confirmed CZS, born between 01 August 2015 and 31 July 2016 in Salvador, BA, Brazil.

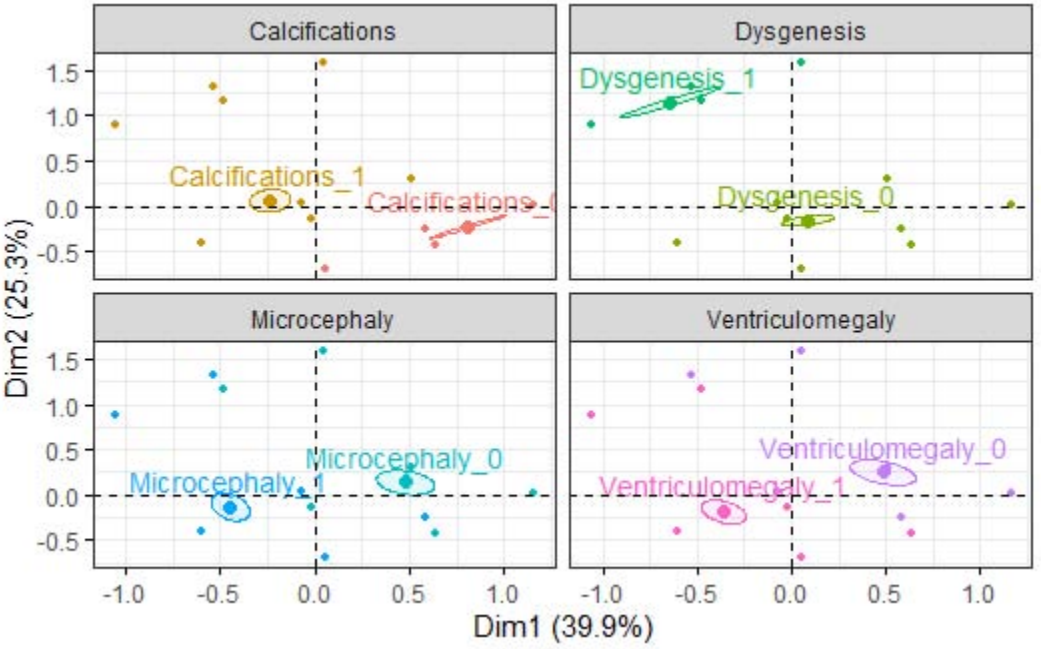
Characteristics	n	%
Period of detection of brain damage (135)		
Intrauterine	48	35.6
Postpartum	87	64.4
Classification according to cephalic perimeter (136)		
Within normal range	66	48.5
Microcephaly (<=-2SD to < -3SD)	26	19.1
Severe microcephaly (<= -3SD)	44	32.4
Brain damages (136)		
Calcifications	105	77.2
Ventriculomegaly	78	57.4
Subependymal Cysts	19	13.9
Dysgenesis of the corpus callosum	16	11.8
Agenesis of the corpus callosum	14	10.3
Hydrocephalus	15	11.0
Lissencephaly	10	7.4

Source: Registro de Eventos em Saúde Pública/ Secretaria Municipal de Saúde de Salvador/ Centro de Informações Estratégicas em Vigilância em Saúde

Table 2: Description of the remaining brain damages variables and percentage of relative contribution values for variability in dimensions 1 and 2 obtained through multiple correspondence analysis.

Variable	Categories [%]	Variability of relative contribution (%)	
		Dimension 1	Dimension 2
Ventriculomegaly	Sim [57.4]	**27.32**	18.14
Calcifications	Sim [77.2]	**30.25**	5.82
Dysgenesis	Sim [11.8]	8.71	68.91
Microcephaly	Sim [51.5]	**33.73**	7.13


Variable categories - MCA
Dysgenesis_1
Ventriculomegaly_0
Microcephaly_0
Calcifications_1
Microcephaly_1
Ventriculomegaly_1
Dysgenesis_0
Calcifications_0
Dim2 (25.3%)
Dim1 (39.9%)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-0.5
0.0
0.5
1.0


Calcifications
Dysgenesis
Microcephaly
Ventriculomegaly
Calcifications_1
Calcifications_0
Dysgenesis_1
Dysgenesis_0
Microcephaly_1
Microcephaly_0
Ventriculomegaly_1
Ventriculomegaly_0
Dim2 (25.3%)
Dim1 (39.9%)
1.5
1.0
0.5
0.0
-0.5
-1.0