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Fetuses with Trisomy 21: Morphological changes in anatomo-pathologic reports

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Fetuses with Trisomy 21:
Morphological changes in anatomo-pathologic reports

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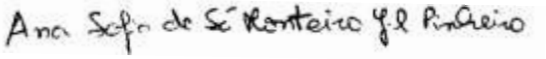

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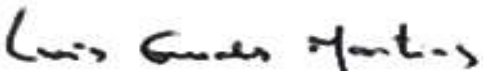

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Resumo

Introdução: A Trissomia 21 é a aneuploidia mais comum em recém-nascidos e a causa mais frequente de défice intelectual. É caracterizada por várias malformações congénitas, dismorfias e múltiplas comorbilidades. No síndrome de Down as alterações cardíacas estão extensamente descritas (46%), seguidas das alterações gastrointestinais (11%). Dismorfias faciais e nas extremidades também são características. O objetivo deste estudo é descrever as alterações morfológicas encontradas em fetos diagnosticados com trissomia 21 e comparar essas frequências com as descritas em trabalhos similares e na literatura.

Material e método: Estudo retrospetivo, realizado entre junho de 2015 e junho de 2020, onde foram incluídas 75 gestantes que requereram a interrupção médica da gravidez após um diagnóstico fetal de trissomia 21. Vários dados foram colhidos, nomeadamente a idade materna, resultados dos testes invasivos e não invasivos e a idade gestacional na qual a interrupção foi realizada. Foram também consultados os relatórios dos exames anátomo-patológicos.

Resultados: No nosso estudo 72 fetos foram autopsiados tendo sido identificadas 344 malformações. As mais comuns foram malformações na cabeça, com uma frequência de 53,78%, seguida pelas extremidades em 27,93% dos casos, alterações genito-urinárias (6,10%), malformações cardíacas (3,20%), pulmonares (3,20%), gastrointestinais (2,33%) e, por último, no sistema nervoso central em 1,45% dos casos. A maioria das malformações descritas encontravam-se no hábito externo.

Conclusão: Em alguns dos sistemas foi possível encontrar correlação com as frequências descritas na literatura, embora não se tenha verificado em todos, nomeadamente no sistema cardiovascular. No entanto observamos, com uma expressão significativa, alterações menos descritas em estudos similares e na literatura, tais como alterações na lobulação pulmonar, dilatação pielocalicial e pé boto.

Palavras-chave: Aborto eugénico; Malformações congénitas; Síndrome de Down

Abstract

Introduction: Trisomy 21 is the most common aneuploidy among liveborn infants and most frequent form of intellectual disability. It is characterized by a variety of congenital malformations, dysmorphic features and multiple health problems. The most common are heart defects (46%), followed by gastrointestinal defects (11%). Facial and extremities features are also frequently described. The aim of this study is to describe the morphological changes found in fetuses diagnosed with trisomy 21 and to compare these frequencies with those described in other similar works and with those described in the literature.

Material and Methods: This was a retrospective study that considered a group of 75 women who had a diagnosis of fetuses with trisomy 21 and required elective termination of pregnancy between June 2015 and June 2020. Maternal age, results of non-invasive and invasive tests, and the gestational age at which the ETP was performed were collected. Anatomo-pathology reports were also consulted.

Results: In our series, 72 fetuses were autopsied and 344 major and minor anomalies were identified. The most common associated anomalies were head abnormalities, with a rate of 53,78%, followed by extremities, with a 27,93% frequency, genito-urinary abnormalities (6,10%), congenital heart defects (3,20%), pulmonary abnormalities (3,20%), digestive abnormalities (2,33%) and, finally, the rate of congenital brain defects was 1,45%. The majority of the anomalies were found in the external habit.

Conclusion: We found agreement to some categories of anomalies associated with DS described in literature, although this was not verified in every system, namely congenital heart defects. Less studied anomalies were also found with significant expression in our population, such as alteration of the pulmonary lobulation, pyelocaliceal dilation and clubfoot.

Keywords: Abortion, Eugenic; Down Syndrome; Congenital Abnormalities

Abbreviations

ß -hCG | Beta human chorionic gonadotropin

µE3 | Unconjugated estradiol

AFP | α-fetoprotein

cfDNA | Cell-free DNA

DS | Down Syndrome

ETP | Elective termination of pregnancy

NT | Nuchal translucency

PAPP-A | Pregnancy-associated plasma protein A

T21 | Trisomy 21

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Introduction

Trisomy 21 (T21) is the most common aneuploidy among liveborn infants. [1] This anomaly is the most frequent form of intellectual disability and is characterized by a variety of congenital malformations, dysmorphic features and multiple health problems. [2,3] These features are not present in every affected individual, and each one has between 6 and 10 characteristics. That is why the impact of Down Syndrome (DS) is different between individuals, with some being deeply impacted while others are healthy and able to live independently as adults.[4]

Several factors have been identified that increase the risk of having a child with this chromosomal abnormality, including previous pregnancy complicated by T21, history of early pregnancy loss and advanced maternal age. A 20-year-old woman has a 1/1480 risk and this incidence increases proportionally with maternal age, reaching 1/85 pregnancies at 40 years of age.[5,6]

Some ultrasound findings are usual in DS, namely increased nuchal translucency (NT), which is the hypoechoic region localized between the skin and soft tissues behind the cervical spine that can be measured between the 11th and 14th gestational week.[7] In almost all fetuses can be identified a small amount of nuchal fluid, but if the value is higher than the 95th percentile it is considered abnormal.[8] This accumulation of fluid happens due to the anomalous content of collagen of the dermis, which hydrophilic properties cause the accumulation of subcutaneous fluid.[9] Another common finding during the 1st trimester is cystic hygroma, which is defined as a congenital malformation resulting from lymph accumulation in the jugular lymphatic sacs due to obstruction of the lymphatic system, most commonly in the fetal neck.[10] Other sonographic findings include slightly shortened humerus or femur, ventricular septal defects, duodenal atresia, ventriculomegaly, echogenic bowel, pyelectasis and hypoplastic or absent nasal bone.[11,12]

The preferred screening test used in Portugal is the combined test of the 1st trimester. It has the highest rates of sensitivity and specificity.[13] The combined test includes two biochemical markers, maternal serum pregnancy-associated plasma protein A (PAPP-A), maternal serum beta human chorionic gonadotropin (ß -hCG or free ß -hCG subunit) that are analyzed between 9 and 13 weeks of pregnancy among with ultrasonographic markers: the size of the NT and the presence or absence of the fetal nasal bone between 11+4 and 14 weeks.[14] If the combined test can not be performed in the 1st trimester, the biochemical screening of the 2nd trimester

can be carried out between 15 and 22 weeks of pregnancy. It includes the measurement of three biochemical markers, of serum α-fetoprotein (AFP), free ß-hCG, unconjugated estradiol (µE3), or four, in addition to those described above, inhibin-A.[15] Another option includes the Cell-free DNA (cfDNA), which evaluates the short segments of fetal DNA found in the maternal blood and is used to screen a variety of fetal conditions.[16] It should be performed from the 10+0 weeks of pregnancy onwards and has the greater sensitivity, about 99%.[17,18] Low risk women can choose cfDNA screening as their primary screening test,[19] but it can be used as a secondary screening test if maternal age is over 35 years old or if ultrasound findings are associated with an increased risk of aneuploidy.[20,21]

In the presence of a 1st or 2nd trimester screening with a positive risk, higher than 1/250, or in cases of positive cfDNA for T21, the pregnant couple is offered the possibility of carrying out an invasive diagnostic test,[22] namely a chorionic villus biopsy between 11 and 13 + 6 weeks of gestation or amniocentesis from the 16th week of gestation on, which are the gold standards for confirming the fetal karyotype,[22] and whose risk of fetal loss is less than 0,5%.[23,24]

Upon diagnosis of DS the majority of couples ask for elective termination of pregnancy (ETP).[25] In Portugal it is possible to perform it up to 24 weeks of gestation,[26] with chromosomal diseases being responsible for about 50% of ETP.[27] However, about 43% of pregnancies end in spontaneous abortion between 10 weeks of gestation and birth, between 16 weeks of gestation and birth this number drops to 23%.[6]

One of the main causes for these fetal demises are fetal malformations, however only 21% of these are detected by ultrasound, which confirms the low incidence of major malformations associated with Down's syndrome as well as the importance of screening tests for their diagnosis and confirmation.[27]

There are numerous clinical manifestations of DS and they can be present in any body system.[3] From all the described malformations, the most common are heart defects (46%), followed by gastrointestinal defects (11%). The most frequent cardiac malformations are atrioventricular canal defects (40-70%), ventricular septal defects and patent ductus arteriosus.[28] Regarding gastrointestinal malformations, the most prevalent are duodenal atresia, Hirschsprung's disease and, finally, tracheoesophageal fistula.[29] Other, less frequent, changes are also described including urinary tract malformations and congenital cataracts.[4,30] Facial features are very usual, and include low-set ears, brachycephaly, short neck, almond-shaped eyes with epicanthic folds, a flat or depressed nasal bridge, an upturned nose, and an open-mouthed facial posture, which may include a protruding tongue.[31] Dysmorphic features of DS also affect

extremities. Those include short broad hands, clinodactyly, single transverse palmar crease, sandal gap and hyperflexibility of joints.[32]

The aim of this study is to describe the morphological changes found in fetuses diagnosed with T21 and to compare these frequencies with those described in other similar works and with those described in the literature.

Materials and Methods

This retrospective study was conducted in the Fetal Medicine Unit of "Centro Materno Infantil do Norte" (CMIN) in Oporto, Portugal, in a group of 75 women who had a diagnosis of fetus with T21 and required ETP between June 2015 and June 2020.

Ethical approval for the conduction of this study was granted by the Ethics Committee of "Centro Hospitalar Universitário do Porto" [2020.292(223- DEFI/263-CE)].

Women who required ETP between that period had been submitted to screening tests in which the risk of having a fetus with DS was greater than 1/250, which was considered significant. Subsequently they were submitted to invasive tests, either chorionic villus biopsy or amniocentesis that confirmed they were effectively cases of Trisomy 21.

From this group three cases were excluded of the study, two of them because the gestational age was over 24 weeks, the limit set by law to perform ETP, and one who decided to do the procedure outside of the hospital as seen in Figure 1.

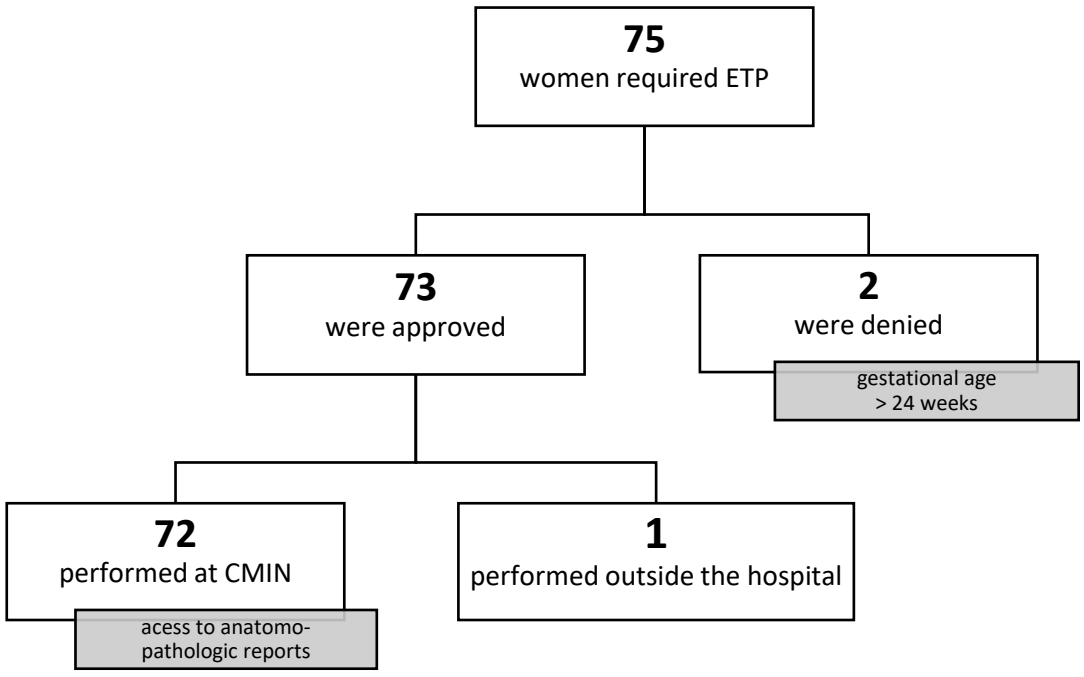

Figure 1 - Organization chart of the studied population

All 72 ETP were performed at CMIN and, subsequently, all fetuses were submitted to an anatomo-pathological study by pathologists at the Centro Hospitalar Universitário do Porto.

In this study, the following data were consulted: maternal age, biochemical screening of the 1st or 2nd trimester, NT value and echographic changes. Results of cfDNA, amniocentesis and chorionic villus biopsy, and the gestational age at which the ETP was performed were also

collected. In relation to the consulted anatomo-pathology reports, all the changes described in the external and internal habits were collected and were separated by systems: head, extremities, cardiovascular, pulmonary, genito-urinary, gastrointestinal and central nervous system.

Data were retrieved from the hospital medical records electronic systems, namely SClínico® and Astraia®. Information was obtained from all available records including cytogenetic files, prenatal consultation records, maternity files and anatomo-pathological reports.

The collected data were organized with Microsoft Excel 2016 for Windows and analyzed with the SPSS – Statistical Package for Social Sciences v.25 also for Windows.

Results

In our study, median maternal age was 36 years. Out of the 75 women, fifty one (68%) were older than 35 years of age as seen in Figure 2. Maternal age ranged from 24 to 48 years old. In none of the cases there was a history of previous pregnancy affected by T21.

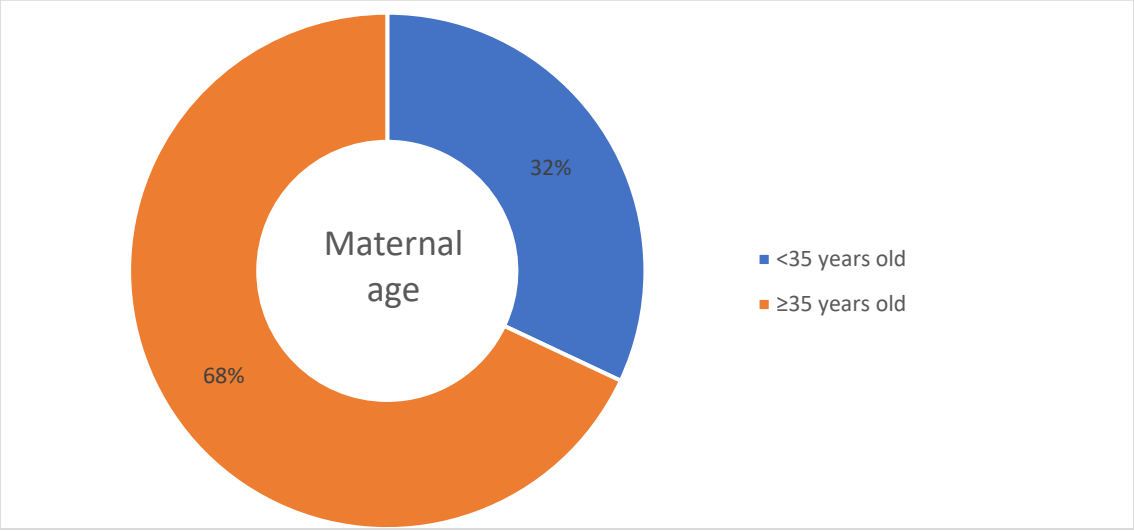

Figure 2 - Maternal age of mothers present in the study

During the five-year study, 75 women were submitted to invasive tests after undergoing screening tests (Figure 3) in which the risk of having a child with DS was greater than 1/250. In 6.2% of cases morphological changes had been detected during ultrasound, namely ventriculomegaly, hydropsy and cardiac changes, namely complete atrioventricular septal defect and tricuspid regurgitation. The positivity of the cfDNA test was the reason of invasive testing in 20.4% of cases, in 33.6% it was due to a positive screening during the 1st or 2nd trimester and, lastly, 39.8% as a result of an increased value of the NT (greater than 95th percentile). Subsequently, amniocentesis was performed in 62,7% of the pregnant woman and 37,3% were submitted to chorionic villus biopsy. In all cases, the suspicion of chromosomal disease was confirmed. When the parents were informed about the confirmation of the diagnosis of DS, was offered the option for ETP to them. After the analysis of the requests by the Ethics Committee, two cases were not accepted because they were over the gestational age allowed by law for this procedure, 24 weeks of gestation, and in another case, despite being accepted, preferred to perform the procedure outside the hospital. In fifty seven (79,2%) cases of ETP the gestational age was under twenty weeks.

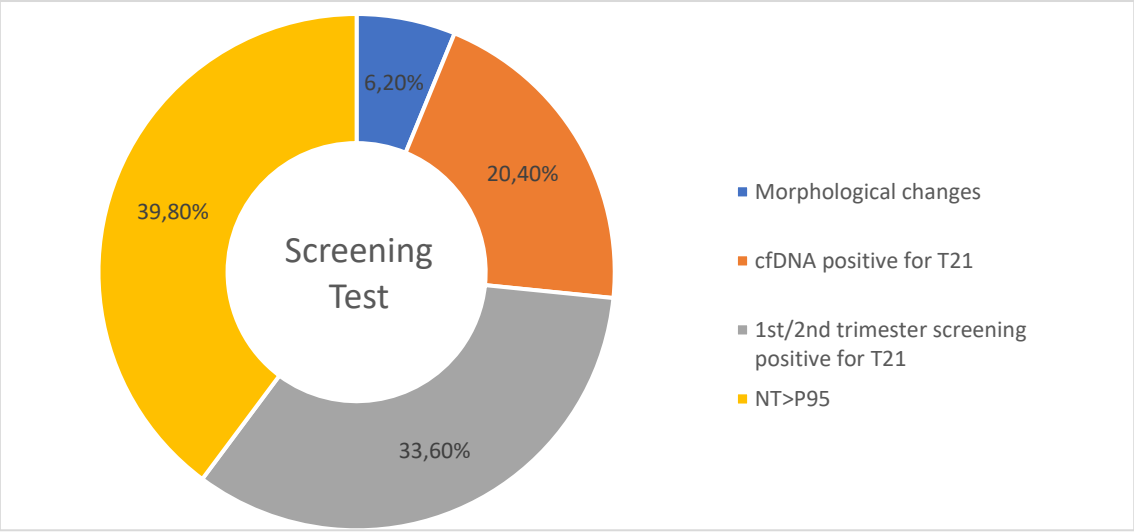

Figure 3 - Reason for being submitted to invasive testing.

In our series, 72 fetuses (X) were autopsied and 344 (N) major and minor anomalies were identified (*Table I - Congenital anomalies seen in our study* – Appendix). All results are represented in descending order.

The most common anomalies were head abnormalities, with a rate of 53,78% (n=185, N=344) of all observed congenital anomalies. Low-set ears was the most common anomaly with a frequency of 54,17% (n=39, X=72). Nuchal edema was the second most common anomaly with 41,67% (n=30, X=72) of cases, followed by hypertelorism with a rate of 31,94% (n=23, X=72), depressed nasal bridge seen in 25% of cases (n=18, X=72), macroglossy observed in 20,83% (n=15, X=72), brachycephaly was described in 19,44% (n=14, X=72), followed by microretrognathia 15,28%, anteverted nares 13,89%, small mouth 12,50%, cystic hygroma 11,11% and wide neck 8,33% (these characteristics were seen respectively in 11, 10, 9, 8 and 6 cases). The rarest head anomalies were upslanting of eyelid fissures and microglossy, both seen once, with a 1,39% rate.

The second most common anomalies were abnormalities of extremities with a rate of 27,03% (n=93, N=344). Short broad hand was the most common anomaly, 55,56% (n=40, X=72), followed by single transverse palmar crease, 38,89% (n=28, X=72). Other anomalies were observed, namely, club foot in 13,89% (n=10, X=72) of all cases, brachydactyly 12,50% (n=9, X=72), clinodactyly 5,56% (n=4, X=72). The least frequent anomalies were prominent calcaneus and overlapping fingers, both seen in one case, with 1,39% rate.

The genito-urinary abnormalities were found with a rate of 6,10% (n=21, N=344). Pyelocaliceal dilatation was reported in 12,50% (n=9, X=72) of cases. Renal hypoplasia was identified in

9,72% (n=7, X=72) of cases. Urethral dilatation was observed in 5,56% (n=4, X=72) of cases. One case of bicornuate uterus was diagnosed, with a rate of 1,39%.

Congenital heart defects were found in 3,20% (n=11, N=344) of all observed congenital anomalies. The interventricular communication was observed at a frequency of 6,94% (n=5, X=72) of cases. Atrioventricular canal defect was identified in 5,56% (n=4, X=72) of cases. However, the less frequent cardiac anomalies were interauricular communication and right atrial enlargement, both seen once, with a rate of 1,39% (n=1, X=72) of cases.

The rate of pulmonary abnormalities was 3,20% (n=11, N=344) of all observed congenital anomalies. Nine cases (%=12,50, X=72) of lung lobation anomalies were reported in our series. Pulmonary hypoplasia was observed in 2.78% (n=2, X=72) of cases.

Digestive abnormalities were observed at the rate of 2,33%. The common mesentery was the most frequent anomaly with a frequency equal to 8,33% (n=6, X=72), followed by duodenal atresia and small bowel diverticula was seen once with a rate of 1,39% (n=1, X=72).

The rate of congenital brain defects was 1,45% (n=5, N=344) of all observed congenital anomalies. Ventriculomegaly was observed in 2,78% (n=2, X=72) of cases. Hydrocephalus was observed in 1,39% (n=1, X=72) of cases, one cerebellar abnormality and one choroid plexus cyst was also detected (1,39% (n=1, X=72).

Finally, hydrops fetalis was observed in 13,89% (n=10, X=72) of cases.

Discussion

Down Syndrome was first described by Down in 1866 and linked to trisomy 21 in 1959 by Lejeune and Jacobs. It is the most common chromosomal abnormality causing intellectual disability with intelligence quotients in the range of 20–85, developmental delay, and multiple physical findings.[21,33]

Nowadays, in Portugal, there is a drop in births of babies with DS. This is due to the higher number of ETP when T21 is diagnosed. It is estimated that in Portugal a baby is born with DS, for every 1000 births. A few years ago the incidence was 1/600 live births.[34]

Currently women are getting pregnant later. DS, as well as other chromosomal abnormalities, increase in frequency with advanced maternal age.[5] In our study 68%, of all pregnant women were 35 years old or older which is coincident with what is described in literature.

As shown in *Table II - Congenital abnormalities presents in our series vs literature* of Appendix, the comparison of our study with other bibliographic sources, allows the following to be stated.

Facial features are one of the most common characteristics of DS.[35] In our series, these abnormalities were the most frequently described, with a rate of 53,78%, of all observed congenital anomalies.

Low-set ears was the most common anomaly with a frequency of 54,17%. In the study of Kava et al. it is present in 66,90% of all cases.[36]

Hypertelorism was also one of the most common anomalies with a rate of 31,94%, which is similar with the study of Kava et al., where he describes this malformation in 33,90% of fetuses,[36] and 33,30% in the series of Azman et al.[37]

Macroglossy was observed in 20,83% of all fetuses, 19,20% in the series of Azman et al.,[37] while in Kava et al. study it was described in 29,90% of all cases, and in the study of Aloui et al. was described in 43,75% of fetuses.[38]

In our study, brachycephaly was described in 19,44% of fetuses, similar to the study of Aloui et al. where they describe this in 14,48% of all cases,[38] but this malformation is more frequent in the studies of Kava et al., 50,90%,[36] and Azman et al., 64,90%.[37]

Microretrognathia and wide neck were observed in 15,28% and 8,33% of all cases, but it has been seen in different frequencies in the series of Kava et al. where it was seen in 2,30% and 36,80% of all cases, respectively.[36]

Cystic hygroma was reported in 8 cases (11,11%), being less frequent in the series of Aloui et al. where it was observed in only 4 cases (2,77%).[38]

Some of the most frequently described head features were not seen in our series, namely upslanting palpebral fissures and epicanthic folds which were described in 89,30% and 17,5% of all cases in the series of Azman et al..[37]

Limb abnormalities was the second most common congenital anomaly with a rate of 27,03%, while in the series of Aloui et al. and Stoll et al. it was described in 31% and 5% of all cases, respectively.[38,39]

In our series, short broad hand was the most common anomaly (55,56%) however it was less frequent in the series of Azman et al. (24,5%).[37]

Single transverse palmar crease was one of the most common anomaly seen in 38,89% of fetuses, which is coincident with other studies. This anomaly was also described in series of Grangé et al. (33%), Kava et al. (33,20%) and Azman et al. (36,80%).[36,37,40]

Club foot was observed in the study of Aloui et al. in 4,86% of cases,[38] and in the series of Grangé et al. in 6% of fetuses.[40] In our series it was more frequent, being observed in 13,89% of all cases.

In the studies of Aloui et al., Azman et al., Kava et al., Guigue et al., Grangé et al. respectively, 9,72%, 19,20%, 36,10%, 37,50% and 71,00% of fetuses have shown a clinodactyly of fifth finger.[36–38,40,41] In our series, this anomaly was less observed, in only 5,56% of fetuses.

Brachydactyly was observed in 12,50% in our study, which is coincident with the series of Kava et al., that described 11,1% of fetuses with this anomaly.[36]

Genito-urinary anomalies were found in a rate of 6,10%. In this group, pyelocaliceal dilatation was the most reported anomaly in 12,50% of cases. In the series of Aloui et al. and Grangé et al. it was seen with frequency of 3,47% and 12%, respectively.[38,40]

Renal hypoplasia and urethral dilatation were identified in 9,72% and 5,56% of cases, although in the series of Aloui et al. these anomalies were reported in 1,38% and 6,25% of fetuses, respectively.[38]

Although congenital heart defects are well established as a consequence of DS, in our series the frequency was not as high as in other series or as in what is described in literature. They are considered to be the most important clinical phenomenon of DS to have a real impact on morbidity and mortality in affected infants.[42] It is also known that the majority of children with

DS presenting with CHD are born from mothers older than 35 years.[37] Despite this, in our study, this was not verified, and the proportion of fetuses affected with cardiac disorders of mothers over 35 years old was equal to those under 35 years old.

Heart defects were seen in 3,20% of all cases, Grangé et al. reported a 42% frequency and Stoll et al. 44%.[39,40] The only that presents frequencies below the average is the study of Aloui et al. who described a 11,18% frequency.[38]

Atrioventricular septal defect and interventricular communication are described in literature as the cardiac anomalies more frequent in fetuses with DS, totalizing 76% of heart defects.[43] In our study, these two anomalies combined equal to 81,82% (n=9, N=11), very similar to the series of Aloui et al., with a frequency of 87,75%.[38]

The atrial septal defect was the least common anomaly with a rate of 1,39%. The percentage of this anomaly in other series ranged from 4,19% (Aloui et al.) to 14,00% (Grangé et al.).[38,40]

Congenital lung abnormalities are not much described in literature. In spite of this, in our study, a rate of 3,20% was detected. It is reported a 2,73% rate in Aloui et al.'s study Lobulation anomalies of the lung was noted in 12,50% of cases in our series. Aloui et al. and Grangé et al. have found these anomalies in a lower frequency, with a rate of 5,55% and 6%, respectively. Additionally, Aloui et al. described pulmonary hypoplasia in 2,08% of cases, resembling our study with a 2.78% rate.[38,40]

In our series, digestive abnormalities were observed at the rate of 2,33%, less frequent than in the series of Stoll et al., with a rate of 6,00%.[39] The common mesentery was the most frequent anomaly with a frequency equal to 8.33%, which is in agreement with what is described by Aloui et al. (10,41%).[38]

Duodenal atresia was seen once with a rate of 1,39%, Grangé et al. described it in 4,00% of all cases.[40]

Concerning the congenital brain defects, we noted 1,45% (n =5, N = 344) of all observed congenital anomalies. Ventriculomegaly was observed in 2,78% (n = 2, X= 72) of cases, which is similar to Grangé et al. (2,00%) and Aloui et al. (3,47%).[38,40]

Hydrocephalus and cerebellar abnormalities were observed in 1,39% (n = 1, X= 72) of cases. Both were observed in a rate of 4,16% in the series of Aloui et al..[38]

Finally, hydrops fetalis is a condition well described in literature.[44] It was observed in 13,89% of cases, much more frequent than in the series of Aloui et al. (0,69%).[38]

Conclusion

In our study, the most common associated anomalies were head abnormalities, with a rate of 53,78%, followed by extremities, with a 27,93% frequency. We found agreement to some categories of anomalies associated with DS described in the literature, although this is not verified in every system, namely congenital heart defects. In addition to all the anomalies already extensively described in literature, less studied alterations were verified in our population, but with an important expression, such as alteration of the pulmonary lobulation, pyelocaliceal dilation and clubfoot. However, an important rate of ETP, 79,2%, was performed under 20 weeks of gestation, which contributed to more subtle morphological findings. The majority of them were detected when the anatomo-pathologic study was performed and only in 6.3% of cases these anomalies were identified during the ultrasound performance, which reinforces the importance of prenatal screening tests and their sensitivity for detecting chromosomal changes.

In order to make this study more homogeneous, in future works, all fetuses should be subject to anatomo-pathologic examination by the same doctor, avoiding interoperator variability. In centers where the incidence of cases is higher, it may also be possible to choose cases within the same gestational week, preventing this from being a bias.

Appendix

Table I - Congenital anomalies seen in our study

	X (fetuses) ***N (total anomalies)***	***72*** ***344***
Head	**n=185**	**53,78%**
Low-set ears	n=39	54,17%
Nuchal edema	n=30	41,67%
Hypertelorism	n=23	31,94%
Depressed nasal bridge	n=18	25,00%
Macroglossy	n=15	20,83%
Microretrognathia	n=11	15,28%
Anteverted nares	n=10	13,89%
Brachycephaly	n=14	19,44%
Small mouth	n=9	12,50%
Cystic hygroma	n=8	11,11%
Wide neck	n=6	8,33%
Upslanting of eyelid fissures	n=1	1,39%
Microglossy	n=1	1,39%
Extremities	**n=93**	**27,03%**
Short broad hands	n=40	55,56%
Single transverse palmar crease	n=28	38,89%
Club foot	n=10	13,89%
Brachydactyly	n=9	12,50%
Clinodactyly	n=4	5,56%
Prominent calcaneus	n=1	1,39%
Overlapping fingers	n=1	1,39%
Genito-urinary	**n=21**	**6,10%**
Pyelocaliceal dilatation	n=9	12,50%
Renal hypoplasia	n=7	9,72%
Urethral dilatation	n=4	5,56%
Bicornuate uterus	n=1	1,39%
Cardiovascular	**n=11**	**3,20%**
Interventricular communication	n=5	6,94%
Atrioventricular canal defect	n=4	5,56%
Interatrial communication	n=1	1,39%
Right atrial dilatation	n=1	1,39%
Pulmonary	**n=11**	**3,20%**
Lung lobation anomalies	n=9	12,50%
Pulmonary hypoplasia	n=2	2,78%
Digestive	**n=8**	**2,33%**
Common mesentery	n=6	8,33%
Duodenal atresia	n=1	1,39%
Bowel diverticula	n=1	1,39%
Central nervous system	**n=5**	**1,45%**
Ventriculomegaly	n=2	2,78%
Choroid plexus cysts	n=1	1,39%
Hydrocephalus	n=1	1,39%
Cerebellar anomaly	n=1	1,39%
Other	**n=10**	**2,91%**
Hydrops fetalis	n=10	13,89%

Table II - Congenital abnormalities presents in our series vs literature

Abnormalities	***Our Study***	***Kava et al.***[36]	***Azman* et al.**[37]	***Aloui et al.***[38]	***Stoll* et al.**[39]	***Grangé et al.***[40]	***Guigué et al.***[41]
Head	**53,78%**						
Low-set ears	54,17%	66,90%					
Hypertelorism	31,94%	33,90%	33,30%				
Macroglossy	20,83%	29,90%	19,20%	43,75%			
Brachycephaly	19,44%	50,90%	64,90%	14,48%			
Microretrognathia	15,28%	2,30%					
Cystic hygroma	11,11%			2,77%			
Wide neck	8,33%	36,80%					
Extremities	**27,03%**			**31,00%**	**5,00%**		
Short broad hands	55,56%		24,50%				
Single transverse palmar crease	38,89%	33,20%	36,80%	56,25%		33,00%	
Club foot	13,89%			4,86%		6,00%	
Brachydactyly	12,50%	11,10%					
Clinodactyly	5,56%	36,10%	19,20%	9,72%		71,00%	37,5%
Genito-urinary	**6,10%**						
Pyelocaliceal dilatation	12,50%			3,47%		12,00%	
Renal hypoplasia	9,72%			1,38%			
Urethral dilatation	5,56%			6,25%			
Cardiovascular	**3,20%**			**11,18%**	**44,00%**	**12,74%**	
Interventricular communication	6,94%			16,66%		13,00%	
Atrioventricular canal defect	5,56%			13,19%		12,00%	
Interatrial communication	1,39%			4,19%		14,00%	
Right atrial dilatation	1,39%						
Pulmonary	**3,20%**			2,73%			
Lung lobation anomalies	12,50%			5,55%		6,00%	
Pulmonary hypoplasia	2,78%			2,08%			
Digestive	**2,33%**				**6,00%**		
Common mesentery	8,33%			10,41%			
Duodenal atresia	1,39%					4,00%	
Central nervous system	**1,45%**			**4,56%**	**0,80%**		
Ventriculomegaly	2,78%			3,47%		2,00%	
Hydrocephalus	1,39%			4,16%			
Cerebellar anomaly	1,39%			4,16%			
Other	**2,91%**						
Hydrops fetalis	13,89%			0,69%			

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