Molar Incisor Hypomineralisation: Possible aetiological factors in children from urban and rural areas

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Abstract

AIM: To analyse factors potentially associated with molar incisor hypomineralisation (MIH) development. **METHODS:** A population-based study was carried out with 903 children aged from 6-12 years old, born and residing in rural and urban areas of the town of Botelhos, State of Minas Gerais, Brazil. Their mothers completed a structured medical history questionnaire, from pregnancy to the child's 3rd year of life. Two examiners evaluated children for MIH according to criteria suggested by the European Academy of Paediatric Dentistry. Descriptive analyses of the data and odds ratios (OR) with 95% test-based confidence intervals (CI) were estimated. Chi-square test was used to evaluate the differences between groups. **RESULTS:** The prevalence of MIH in children from rural area (RA) was significantly higher than those from the urban area (UA) (24.9% versus 17.8%, p= 0.01). In urban children, neither significant associations with MIH nor medical problems were found. In rural children, however, MIH was significantly more common among those whose mothers had experienced medical problems during pregnancy (OR=2.11; 1.01-4.37 CI 95%; p=0.04), who had throat infections (OR=2.93; 1.47-5.87 CI 95%; p=0.01), who had high fever (OR=1.91; 1.07-3.39 CI 95%; p=0.02), and who had used amoxicillin associated with other antibiotics (OR=1.92; 1.02-3.62 CI 95%; p=0.04) during the first 3 years of life. **CONCLUSION:** This study suggests a link between MIH and health problems during pregnancy, as well as environmental factors.

Introduction

Molar incisor hypomineralisation (MIH) is a dental enamel defect of systemic origin, which affects one to four permanent first molars, frequently associated with incisors [Weerheijm et al., 2001]. Clinically, hypomineralisation may vary from demarcated opacities to structural loss [Weerheijm et al., 2003]. Usually, severely affected molars may chip easily after their eruption or under masticatory forces, leading to unprotected dentine and unexpectedly fast development of caries [Weerheijm et al., 2001 and 2003].

As paediatricians are often the first professionals to take care of children's health, the physician/dentist interaction may contribute to early diagnosis of such tooth defects. Permanent first molars and incisors erupting about the age of 6-7 years can be affected, and children may experience severe tooth sensitivity [Weerheijm et al., 2001]. Early diagnosis and prevention can help eliminate significant dental complications and reduce the risk of decay in later childhood.

The aetiology of MIH is still unclear and the exact nature of the systemic insult is poorly defined. Many factors have been related to the origin of MIH, such as medical problems during pregnancy, pre-term delivery, long term breast feeding, low-birth weight, diseases of early childhood, respiratory disease, frequent antibiotic use, high fever, hypocalcaemia, and dioxins [Johnsen et al., 1984; Seow et al., 1987; Alaluusua et al., 1996; Jälevik and Norén, 2000; Beentjes et al., 2002; Whatling and Fearne 2008; Laisi et al., 2009]. The association of each factor with MIH is difficult to establish as many of the events can happen more than once during early childhood.

In order to discover possible aetiological factors for MIH, the time at which the defective enamel is formed should be considered and also how to obtain indications of the severity and duration of the insult. According to Alaluusua [2010], the enamel formation has been divided into three major stages. At the secretory stage, ameloblasts secrete large amounts of enamel matrix proteins within which long thin ribbons of enamel mineral, mainly hydroxyapatite, are formed almost immediately the enamel matrix is laid down. During the secretory stage, the enamel crystals grow primarily in length and the enamel layer grows in thickness. The maturation stage begins when the enamel thickness is completed, and the secretory ameloblasts transform, through a short transition stage, into mature ameloblasts responsible for enamel matrix degradation, followed by massive mineralisation of the enamel. At the final mineralisation, the enamel layer hardens as the crystallites grow in width and thickness, resulting in a mineralised tissue that contains more than 95% mineral by weight.

The first permanent molars start to develop during the fourth month of gestation. The four cusps become united at about six months of age, and during the first year the deposition of enamel matrix is completed in the occlusal half of the crown and then maturation is initiated [Suga, 1989; Alaluusua, 2010]. Suckling [1980] suggested that opacities are a qualitative defect of the matrix formed by disorders involving ameloblasts during the stage of enamel maturation. Thus the most critical period for enamel defects of first permanent molars and incisors is during the last months of pregnancy until a child's first year of life [Weerheijm et al., 2001].

There are a few studies of MIH in the Brazilian population [Soviero et al., 2009; Costa-Silva et al., 2010]. A previous population-based study showed prevalence rates of 24.3% and 17.6% in rural and urban children, respectively

[Costa-Silva et al., 2010]. However, knowing the possible aetiological factors are important to determine treatment and public health guidelines as well as the potential causes of MIH, which could explain the higher prevalence among children from rural area. Thus, the aim of the present study was to determine the potential factors involved in the development of MIH in children aged 6-12 years old who live in urban and rural areas of Botelhos in Brazil.

Materials and methods

This study was approved by the research ethics committee of the Araraquara School of Dentistry (FOAr- UNESP) and signed informed consents were obtained from the children's parents. The study was ethically conducted in accordance with the Declaration of Helsinki.

The study was performed with school children from public schools, aged 6-12 years old, and living in urban (Group UA) and rural (Group RA) areas of Botelhos, State of Minas Gerais, Brazil. The town has slightly over 15,000 inhabitants and a Human Development Index (HDI) of 0.7 [Costa-Silva et al., 2010], with medical assistance being provided by the public health service for urban and rural areas although it is mostly concentrated in the former. The natural level of fluoride in the rural community water supply was below 0.1 ppm F, and the ion concentration in the urban community water supply after fluoridation was 0.7 ppm F.

Parents of 1,315 children received a letter informing them of the study together with a structured medical history questionnaire inviting participation of their children in this study. After their parents signed the informed consent form, the children were examined in the in school according to the World Health Organization (WHO) guidelines for epidemiological studies on oral health [1997]. The study sample included only children with all first permanent molars and permanent incisors fully erupted. Children were excluded if their mothers had not lived in Botelhos during their pregnancy, presented with syndromes associated to dental enamel malformation, dental fluorosis, amelogenesis imperfecta or were undergoing orthodontic treatment with fixed appliances. Children attending with other family members, adoptive parents, or other legal guardians were also excluded to ensure that the questions on medical history could be answered as factually as possible.

The dental examinations were performed according to the MIH judgment criteria of the European Academy of Paediatric Dentistry [Weerheijm et al., 2003]. The examiner's training methods and the reliability of the clinical recordings were previously described by Costa-Silva et al. [2010]. The questionnaire was validated with a pre-test conducted with 25 mothers who accompanied their children at the routine dental office visit. The questionnaire was given to the children's parents, who had to complete it at home and then mail it back the next day. They were instructed on how to complete the questionnaire, thus ensuring that answers could be reliably obtained. There were over 30 questions relating to the child's medical history up to their third year of live. The questions were divided into sections aimed at obtaining information about pregnancy, type of delivery, birth weight and prematurity (≤ 7 months), breastfeeding, disease (any diagnosed health problems), use of antibiotics, high fevers (≥ 39°C) and infections during early childhood, as described in previous studies [Koch et al., 1987; Alaluusua et al., 1996; Jälevik and Norén, 2000; Jälevik et al., 2001; Beentjes et al., 2002; Whatling and Fearne, 2008; Laisi et al., 2009].

Data from questionnaires were coded and analysed using the Statistical Package for Social Sciences 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Descriptive data analysis and odds ratio with 95% confidence interval (CI) were estimated. Chi-square tests and Mantel-Haenszel tests were used to evaluate differences between both groups at a significance level of 0.05.

Results

A total of 1,126 children (85.6% of all enrolled children) were examined. Among those children, 208 were excluded for not meeting the inclusion criteria and 15 were excluded for not returning the questionnaire. Overall, 903 children fulfilled the study criteria (80.2%), of which 67.1% (n = 606) were from Group UA and 33.8% (n = 297) were from Group RA.

The percentage of children who had at least one first permanent molar with MIH was 19.8%. The prevalence of MIH

Table 1. *Characteristics of the Brazilian study group, odds ratio (OR), 95% confidence intervals (CI), and p values.*

	Children with MIH		Children without MIH		Total		Odds ratio (95% CI)	p
Variables	n	%	n	%	n	%		
Gender								
Male	90	22.6	305	77.4	395	100	1.31	0.14
Female	92	18.3	416	81.7	508	100	(0.91-1.81)	
Residence areas								
Rural Area (RA)	74	24.9	223	75.0	297	100	0.65	0.013*
Urban Area (UA)	108	17.8	498	82.1	606	100	(0.46-0.91)	

** Statistically significant association, Chi-square test, p<0.05.*

Table 2. *Distribution of variables in MIH in Brazilian children related to mother's health status during pregnancy from urban area (Group UA) and rural area (Group RA), odds ratio (OR), 95% confidence intervals (CI), and p values.*

Variable	Children with MIH			Children without MIH			Odds ratio	95% CI	p
	Total	Yes	%	Total	Yes	%			
Group UA									
Health problems during pregnancy	108	9	8.3	492	42	8.5	0.97	0.45–2.06	0.945
Anaemia	107	4	3.7	492	12	2.4	1.55	0.49–4.91	0.453
Other	107	2	1.8	492	8	1.6	1.15	0.24–5.50	0.859
Caesarian delivery	102	51	50	482	252	52.2	0.91	0.59–1.39	0.675
Smoking	108	25	23.2	498	104	20.9	1.14	0.69–1.87	0.602
Medicines	106	49	46.2	488	226	46.3	0.99	0.65–1.51	0.987
Antibiotics	104	73	70.2	488	381	78.0	0.66	0.41–1.06	0.086
Group RA									
Health problems during pregnancy	74	14	18.9	221	22	9.9	2.11	1.01–4.37	0.045*
Anaemia	74	3	4.0	221	6	2.7	1.51	0.36–6.21	0.565
Other	74	3	4.0	221	3	1.3	3.07	0.60–15.55	0.175
Caesarian delivery	72	44	61.1	218	111	50.9	1.51	0.88–2.60	0.134
Smoking	74	15	20.2	223	43	19.2	1.06	0.55– 2.05	0.853
Medicines	72	38	52.7	221	109	49.3	1.14	0.67–1.95	0.611
Antibiotics	71	59	83.0	221	163	73.7	1.74	0.67–1.95	0.112

** Statistically significant association, Mantel-Haenszel test, p< 0.05.*

was 17.8% (n = 108) in Group UA and 24.9% (n = 74) in Group RA, being significantly higher in the latter (p=0.013). The association analyses were performed separately for each group with odds ratio with 95% confidence intervals (CI). Table 1 shows the characteristics of the groups.

Table 2 shows the bivariate analyses between the prevalence of MIH and mother's medical history during pregnancy. The prevalence of maternal medical problems during pregnancy was 16.8% and 28.8%, respectively, in mothers from urban and rural areas. In Group RA, a statistically significant association was found between MIH and maternal health problems during pregnancy (p=0.045).

Table 3 presents the bivariate analyses between MIH and medical conditions in the first three years of life in Group RA. Factors related to children, such as birth weight, jaundice, childhood health problems, infections, allergies, and antibiotic use showed no statistically significant association with MIH. Moreover, 61.1% (37.8 of children with MIH and 23.3 without MIH) of Group RA and 23.1% (21.5 of children with MIH and 1.6 of children without MIH) of Group UA had diseases in the first 3 years of life (Tables 3 and 4). For Group RA, 35.1% of the children with MIH had high fever (OR=1.91; 1.07-3.39 CI), which was statistically significantly different from the children without MIH (p=0.027) (Table 4), whereas 18% of the children with MIH had suffered from throat infection (OR=2.93; 1.47-5.87 CI), which was also statistically significantly different from the children without MIH (p=0.002).

Statistical differences related to the use of amoxicillin associated with other antibiotics were observed, as reported by mothers of children with and without MIH (p=0.042) in Group RA (Table 4). With regard to low birth weight and breast feeding in terms of duration and habits, there were no significant differences between children with or without MIH (p>0.05).

Discussion

Most of the investigations concerning the aetiology of MIH have been retrospective, cohort or case-control studies [Alaluusua et al., 2010]. They collected a wide variety of factors, such as long term breast feeding, high fevers, respiratory disease, premature birth, antibiotic use, dioxins, and systemic diseases that occurred during critical tooth development: prenatal, perinatal, and postnatal periods [Koch et al., 1987; Alaluusua et al., 1996; Jälevik and Norén, 2000; Jälevik et al., 2001; Beentjes et al., 2002; Whatling and Fearne 2008; Laisi et al., 2009; Fagrell et al., 2011].

MIH prevalence was significantly different between children born and living in rural compared with urban areas (p=0.013) [Costa-Silva et al., 2010]. It is reasonable to assume that the possible factors involved with MIH might be different

Table 3. Distribution of variables in MIH in Brazilian children related to urban area (Group UA) health status, odds ratio (OR), 95% confidence intervals (CI), and p values.

Variable	Children with MIH			Children without MIH			Odds ratio	95% CI	p
	Total	Yes	%	Total	Yes	%			
Perinatal Period									
Birth weight: below 2.500 Kg	106	9	8.5	484	60	12.4	0.65	0.31–1.36	0.260
More than 3.500Kg	106	26	24.5	484	130	26.8	0.88	0.54–1.43	0.622
Premature birth (≤ 7 months)	108	1	0.9	492	33	6.7	0.13	0.18–0.96	0.046
Jaundice	6	4	66.6	46	26	56.5	1.53	0.25–9.25	0.638
Postnatal Period									
Habits	108	89	82.4	494	415	84.0	0.89	0.51–1.54	0.683
Teething rings	108	10	0.9	491	78	15.9	0.54	0.27–1.08	0.082
Feeder	108	74	68.5	492	332	67.4	1.04	0.67–1.64	0.834
Pacifier	108	89	82.4	494	415	84.0	0.89	0.51–1.54	0.683
Habits (> 12 months)	102	71	69.6	460	324	70.4	0.96	0.60–1.53	0.869
Breast feeding	107	90	84.1	492	408	82.9	1.09	0.61–1.92	0.767
Breast feeding (> 7 months)	107	62	57.9	485	296	61.0	0.87	0.56–1.33	0.522
Health problems	108	23	21.5	488	8	1.6	0.81	0.49–1.34	0.418
Pneumonia	107	3	2.8	492	8	1.6	1.74	0.45–6.69	0.417
Bronchitis	107	12	11.2	485	41	8.4	1.36	0.69–2.70	0.367
Rhinitis	95	14	14.7	422	78	18.4	0.76	0.41–1.41	0.389
Trauma	107	26	24.2	493	132	26.7	0.87	0.54–1.42	0.598
High fever (≥ 39°C)	107	29	27.1	487	132	27.1	1.00	0.62–1.60	1.000
Infections	106	11	10.3	489	88	18.0	0.52	0.27–1.02	0.060
Throat infection	104	16	15.3	472	75	15.9	0.96	0.53–173	0.898
Amoxicillin associated with other antibiotics	92	51	55.4	404	245	60.6	0.80	0.51–1.27	0.359
Penicillin only	92	44	47.8	404	208	51.4	0.86	0.54–1.35	0.527
Allergies	56	20	35.7	252	105	41.6	0.77	0.42–1.41	0.413

** Mantel-Haenszel test, p<0.05.*

in populations from rural and urban areas, which helps to explain some of the findings of this study. This was shown in the differences in the prevalence of health problems during pregnancy (28.8% in Group RA and 16.8% in Group UA) and prevalence of health problems experienced by children in the first 3 years of life, 61.1% (37.8 of children with MIH and 23.3 without MIH) of Group RA and 23.1% (21.5 of children with MIH and 1.6 without MIH) of Group UA.

Medical problems such as maternal diabetes, hypertension, drug use, medications, hypercalcaemia, and others during the prenatal period might also have potential associations with MIH together with systemic conditions and poor general health [Chowdhury and Bromage, 2000; Jälevik and Norén, 2000; Kuscu et al., 2008; Lygidakis et al., 2008; Alaluusua et al., 2010]. In the present study, MIH was significantly more common among those children whose mothers lived in rural areas and had experienced health problems during pregnancy (p=0.045). However when the results were linked to specific diseases such as anaemia, hypertension, and diabetes, no significant differences were found between children with MIH and those without MIH.

Although about 50% of the mothers had smoked tabacco during pregnancy, no association was found between MIH and smoking habits. In a laboratory study, Chowdhury and Bromage [2000] observed in rats that foetal exposure to nicotine adversely affected the development of the first permanent molar, including perturbations in the cellular environment (calcium levels, growth factors, and cell signaling). With regard to the perinatal factors, MIH was not associated with premature birth, mode of delivery, low-birth weight, or

Table 4. *Distribution of variables in MIH in Brazilian children related to rural area (Group RA) health status, odds ratio (OR), 95% confidence intervals (CI) and p values.*

Variable	Children with MIH			Children without MIH			Odds ratio	95% CI	p
	Total	Yes	%	Total	Yes	%			
Perinatal Period									
Birth weight: below 2.500 Kg	72	9	12.5	214	25	11.6	1.08	0.47–2.43	0.853
More than 3.500Kg	72	16	22.2	214	48	22.4	0.98	0.52– 1.87	0.970
Premature birth (≤ 7 months)	73	6	8.2	220	7	3.1	2.72	0.88–8.38	0.081
Jaundice	7	2	28.5	9	2	22.2	1.40	0.14–13.56	0.772
Postnatal Period									
Habits	73	66	90.4	223	187	83.8	1.81	0.77–4.27	0.173
Teething rings	73	5	6.8	223	155	69.5	0.03	0.01–0.08	0.001
Feeder	73	58	79.4	223	155	69.5	1.69	0.89–3.20	0.103
Pacifier	73	66	90.4	223	187	83.8	1.81	0.77–4.27	0.173
Habits (> 12 months)	66	42	63.6	205	142	69.2	0.77	0.43–1.39	0.395
Breast feeding	73	60	82.1	223	183	82.0	1.00	0.50–2.01	0.980
Breast feeding (> 7 months)	74	43	58.1	219	135	61.6	0.86	0.50–1.47	0.590
Health problems	74	28	37.8	223	52	23.3	2.00	1.14–3.51	0.160
Pneumonia	74	4	5.4	221	4	1.8	3.10	0.75–12.72	0.116
Bronchitis	74	6	8.1	222	10	4.5	1.87	0.65–5.33	0.242
Rhinitis	56	4	7.1	186	16	8.6	0.81	0.26–2.55	0.728
Trauma	71	18	25.3	219	56	25.5	0.98	0.53–1.83	0.971
High fever (≥ 39°C)	74	26	35.1	222	49	22.0	1.91	1.07–3.39	0.027
Infections	74	14	19.4	220	37	16.8	1.19	0.60–2.36	0.611
Throat infection	72	18	25	216	22	10.1	2.93	1.47–5.87	0.002
Amoxicillin associated with									
other antibiotics	60	43	71.6	185	105	56.7	1.92	1.02–3.62	0.042
Penicillin only	60	34	56.6	185	86	46.4	1.50	0.80–2.70	0.172
Allergy	45	23	51.1	126	50	39.6	1.58	0.80–3.15	0.185

** Statistically significant association, Mantel-Haenszel test, p<0.05.*

neonatal jaundice. This is in agreement with some previous studies [Jälevik et al., 2001; Beentjes et al., 2002; Whatling and Fearne, 2008; Crombie et al., 2009], who reported the difficulties with finding MIH-specific aetiological factors due to the co-existing or closely related nature of many of these putative factors (e.g. premature birth and low birth weight). On the other hand, other studies showed an association between enamel defects and perinatal problems [Johnsen et al., 1984; Seow et al., 1987; Aine at al., 2000; Chowdhury and Bromage, 2000; Lygidakis et al., 2008;]. van Amerongen and Kreulen [1995] found that premature birth, prolonged delivery, and cyanosis were present in 48% of the children with MIH.

With regard to the postnatal period, health problems could disturb the ameloblastic activity during enamel mineralisation because of direct pathological influence or hypoxia, respiratory disease, hypocalcaemia, fever, and malnutrition [Chowdhury and Bromage, 2000; Jälevik et al., 2001; Lygidakis et al., 2008]. In the present study, Group RA had more disease history, including pneumonia, bronchitis, rhinitis, and others (61.1%), than Group UA (23.1%). This may be explained by the social, cultural and nutritional condition of the rural communities, in addition to the more limited access of the rural population to public health services.

The prevalence of high fever and throat infection was significantly different between children with MIH and those without MIH in the Group RA (p=0.027 and p=0.002, respectively). Similar findings were reported by Beentjes et al. [2002], who found that the presence of infections and high fever during the first 4 years of life was higher in children with MIH.

Although the presence of throat infection and the use of amoxicillin associated with other antibiotics were similar between the groups, its distribution was different between children with MIH and without MIH. We agree with authors such as Lygidakis et al. [2008] and Alaluusua [2010], who suggested that enamel defects are the result of a combined effect of several factors. Thus, it is suggested that the Group RA had been exposed to other factors that contributed to the enamel defect.

The association of high fever with enamel hypomineralisation during infancy has recently been explained by an experimental study showing that persistent high fever influenced the process of enamel formation, producing disorientation of enamel prisms and crystal-free areas [Tunk et al., 2006]. Scarfone et al. [2000] explained that febrile seizures were apparently associated with MIH due to an association between febrile conditions and infant hypocalcaemia.

Early studies associated antibiotic use with enamel defects [Jälevik and Norén, 2000; Jälevik et al., 2001; Beentjes et al., 2002; Hong et al., 2005; Laisi et al., 2009], although the results were controversial. Hong et al. [2005] found that amoxicillin use during the first year of life increased the risk of fluoride-like defects in permanent incisors and permanent first molars. Laisi et al. [2009] showed that amoxicillin use in this same period might increase the risk of MIH. In the present study, it was shown that amoxicillin associated with other antibiotics had a significant difference in the Group RA (p=0.042). However, when amoxicillin was the only antibiotic used, no association was found with MIH. This result is not corroborated by Whatling and Fearne [2008], who found that the prevalence of MIH was higher among children who took only amoxicillin during the first 4 years of life. No association however, was found in children taking mixed antibiotics, including amoxicillin. In an experimental study in rats, Laisi et al. [2009] dissected tooth embryonic explants on day 18. Teeth were cultured for 10 days with/without amoxicillin. Ameloblasts of the control molars and those with low exposure to amoxicillin exhibited normal patterns of amelogenesis, whereas ameloblasts of molars exposed to amoxicillin showed altered patterns of amelogenesis, which might interfere with mineralisation. On the other hand, the occurrence of infection, antibiotic use, and high fevers have been strongly correlated with MIH, thus it was not possible to distinguish whether MIH was related to either illness or medication [Jälevik et al., 2001].

Enamel defects have also been associated to the exposure of dioxins or PCBs (polychlorinated dibenzo-p-dioxins) during early childhood. PCBs are persistent polyhalogenated aromatic hydrocarbons that are widespread environmental contaminants [Alaluusua et al., 1996; Jan et al., 2007]. Alaluusua et al. [1996] observed a significant correlation between MIH and the exposure of children to dioxins via mother's milk. However, in the present study, no difference between the groups was found regarding breast feeding, thus corroborating some earlier studies [Jälevik and Norén, 2000; Beentjes et al., 2002; Whatling and Fearne, 2008]. In this study, it was speculated that the presence of some habits in the first three years of life such as the use of pacifiers, feeder and teething rings due to their composition and possible exposition to dioxins, such as bisphenol A, were associated with MIH. However, no association was found between these habits and MIH presence in both groups in the present study, except for the use of teething ring in the RA Group. Due to absence of data in the literature we suggest that this issue should be investigated in further studies.

Retrospective information should be considered when considering aetiological factors, but the design of the present study may have been biased by maternal recall although children who were attending with other family members, adoptive parents, or other legal guardians to ensure that the questions were answered as factually as possible were excluded. A previous study tried to minimise the recall bias by obtaining children's medical notes, but only 60% of the doctors cooperated and the medical notes were too briefly worded to be of use [van Amerongen and Kreulen, 1995]. Prospective studies are needed to improve the level and strength of the evidence on the role of such putative factors and to reveal new factors that may be involved [Aine et al., 2000; Jälevik and Norén, 2000; Alaluusua et al., 2010].

Conclusions

Considering the limitation of the study design, it was concluded that: Environment is important for analysis of the factors involved in MIH and there was an association between medical history problems during pregnancy and MIH. In addition throat infection, high fever, and amoxicillin associated with other antibiotics were linked with MIH, although it is impossible to isolate these factors. Prospective studies and animal experiments are needed to improve the knowledge about amelogenesis and MIH formation.

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