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## **Title page**

### **Title**

Local teratogenic factors and high frequency of Japanese folklore cyclops (*yōkai*)

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### **Abstract**

**BACKGROUND:** Japan is famous for its fabulous creatures (*yōkai*) characterized by their deformities.

**METHODOLOGY:** We wanted to know if local factors were involved in the high frequency of these legendary malformations, and sought to identify local teratogenic elements.

**RESULTS/DISCUSSION:** Many potential teratogenic elements have been identified, which can be linked to specific malformations (cyclopia, for example).

**CONCLUSION/PERSPECTIVES:** We therefore confirm that local factors would indeed promote the development of cyclops in Japan. This might explain the great frequency of supernatural creatures exhibiting this physical characteristic within Japanese folklore, and who would transmit this empirical knowledge through the generations.

### **Keywords**

Ophthalmology; retrospective diagnosis; teratology;

### **Funding**

None.

### **Conflict of interest**

None for any of both authors.

## **Abstract**

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Are there local factors that would promote the development of cyclops in Japan? This might explain the great frequency of supernatural creatures exhibiting this physical characteristic within Japanese folklore. To what extent do ancient traditions, classical texts and folklore make it possible to reconstitute the state of health of the past populations, and even still the present environmental and health context, in continuity with previous conditions? This is what we will try to see with this short scientific research associating literature, social anthropology and biomedical data.

*Yōkai* are a group of liminal beings in Japanese folklore, including spirits, demons, and monsters. They are at least known since the 10<sup>th</sup> century in this chrono-cultural context. The word *yōkai* in Kanji can mean anything between bewitching, catastrophe, mystery, and suspicion. Japanese folklorists explain the idea of *yōkai* as an umbrella term to describe any being that appears strange and mysterious. They are very important, occupying space and time with a marvelous aspect that allows us to better understand some mysterious phenomena, to protect sacred spaces, to delimit the border between the world of humans (civilization) and that of nature. One of the most famous *yōkai* is *Hitotsume kozō*, characteristically depicted as a bald-headed child with only one eyeball in the middle of his forehead, a large red tongue, and shown to be wearing tiny robe reminiscent of Buddhist monks (Figure 1). In folklore and collective memory, he is usually considered harmless, interested only in frightening late-night travelers on dark streets [1].

Other *yōkai* with the same characteristic have been reported in Japanese stories and legends [2]: *Bakezōri* (a sandal-monster), *Dorotabō* (a man in rice mud), *Hitotsume (Dai)nyūdō* (a giant monk), *Hyakkiagyō* (demons), *Ichimoku nyūdo* (a monk), *Ippon datara* (a giant monster with one leg), *Kasabaké* (an umbrella-monster with one leg), *No'uma* (a man-eating nocturnal monster), *Seko* (a child of 2 or 3 years old), *Yagyō-*

*san* (a bearded ogre), *Yama jiji* (an old man), etc. among others. It is interesting to note that the physical description of all these *yōkai* beginning with *hitotsume kozō* – a single eye in the center of the forehead – is compatible with the rare and lethal diagnosis of cyclopia (also cyclocephaly or synophthalmia).

Of course, there are Cyclops individuals in other civilizations, starting with Greco-Roman Antiquity, but also with Balor (one-eyed deity in Irish Celtic mythology), Tartaro (cyclops in Basque mythology, in the Pyrenees between France and Spain), or Likho (one-eyed creature, personification of bad luck in Slavic mythology).

Cyclopia is a form of holoprosencephaly, a congenital disorder, which typically presents itself as single eye or a partially divided eye in a single orbit, and a missing nose (sometimes replaced with a proboscis) [3]. The congenital deformity occurs between the 18<sup>th</sup> and the 28<sup>th</sup> day of gestation [4], when the prosencephalon fails to divide the orbits of the eye into two cavities due to incomplete morphogenesis of fore brain [5]. Sonic Hedgehog Gene Regulator (SHH) is responsible for the bilateral field of the eye, and an SHH mutation usually results in a single eye in the center of the face. Holoprosencephaly occurs in 1/16,000 live births, and 1/250 during embryogenesis. Approximately 1.05 in 100,000 births are identified as infants with cyclopia, including stillbirths. While embryos that develop cyclopia often don't survive pregnancy, cases of live births have been sporadically reported with death occurring within hours of birth [6]. The idea of *Hitotsume kozō* seems to have been a way to deal with what was then an unexplained and mysterious medical condition.

If not of chromosomic origin, ingestion of *Veratrum californium* on the 14<sup>th</sup> day of gestation of mammals is currently recognized as a major cause of cyclopean development in the fetus/embryo. Maybe other agents (botanical? environmental?) at the origin of perturbations in levels of steroidal alkaloids (jervine, cycloamine, cyclo-

sporine, for example) could be involved in development of cyclopia: cold/heat, UV light, radiation/X-ray, hyperbaric pressure, lithium/magnesium intoxication, hypoxia, toxic agent (NaCN ethyl alcohol, phenol, colchicine, nicotine, antibiotics, etc.), viral/bacterial/parasitic infections, hypovitaminoses (folate), hypervitaminoses A, stress, high maternal/paternal age, etc [7,8].

This very large concentration of Japanese folklore cases seems to suggest the existence of factors causing a greater frequency of the disease in this geographical and chrono-cultural context. But with what causes? Endogamy? Taking toxic substances (botanicals or minerals, accidentally, for example with cosmetics or textile pigmentation)? The implication of the diet (seaweed or other seafood, mushrooms, sauces, etc.)? This over-representation of cyclopia is found in ancient literature, but not in contemporary clinical and fetopathological statistics [8] : which would tend to mean that something happened ... which no longer applies today. Future studies will be needed to confirm the epidemiological correlation in actual populations, and to highlight any facilitating environmental factors.

Taking into account local traditions, regional stories and legends linked to very specific territories is essential in medicine: it makes it possible to highlight local factors influencing the health of inhabitants, and knowledge of which has been preserved from one generation to the next in an empirical, literary way, sometimes distorted but always based upon a background of truth. This Japanese example demonstrates, if need be, the value of comparing sources from the human sciences (literature, philology, history, ethnology and ethnography, religious history, art history, anthropology) and fundamental sciences (toxicology, teratology, embryology, endocrinology, etc.) for a global vision of the ecology of diseases and their place in the environment.

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## Legend of figure

**Figure 1.** *Hitotsume-kozō* from the *Bakemonochakutōchō*, circa 1788.

