It is unclear whether he was taken from his Portuguese parents or left freely, but at just eight years old, John lived apart from his parents. He then led an irregular life in Spain and worked at various times as a shepherd, an estate manager, a book seller, and a soldier.

His conversion at age 40 took such extreme forms—including beating himself in public while confessing his sins—that he was temporarily confined for lunacy. While confined, he began to serve other patients. In 1538, he began hospital work caring for the impoverished sick, begging for the supplies needed. He devoted himself to sheltering and caring for the needy, including prostitutes and vagabonds. While he experienced persecution at first, this work eventually brought him respect and renown.

He died on his 55th birthday, after which his companions who had joined him in service were organized into the Hospitaller Order of the Brothers of St. John of God.

John of God is the patron of booksellers, firefighters, hospitals, nurses, and the sick.